VOLUME 98 • C OBER 1959 • NUMBER 4

DISEASES OF CHILDREN

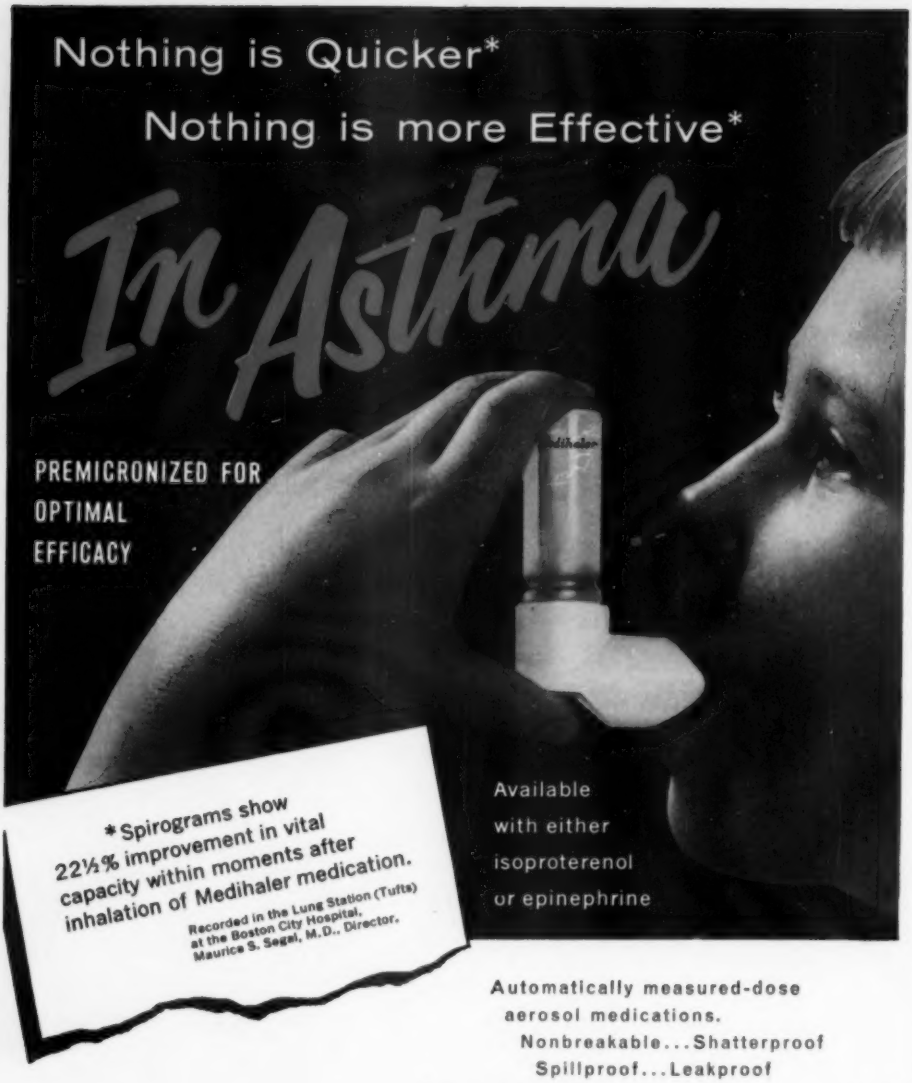
American Pediatric Society

Sixty-Ninth Annual Meeting

May 6, 7, and 8, 1959

Buck Hill Falls, Pa.

AMERICAN MEDICAL ASSOCIATION PUBLICATION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A. M. A.
Journal of Diseases of Children

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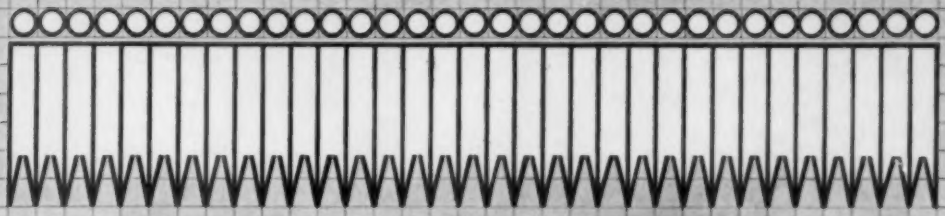

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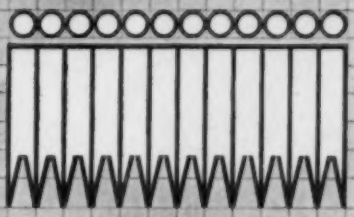

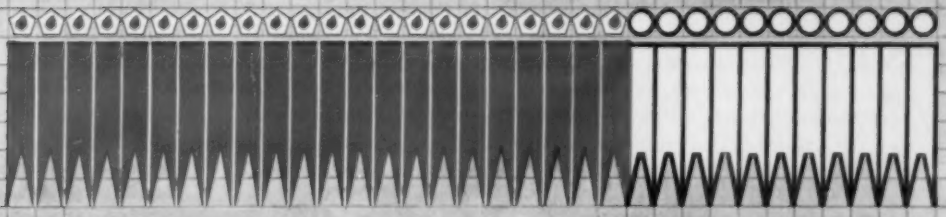

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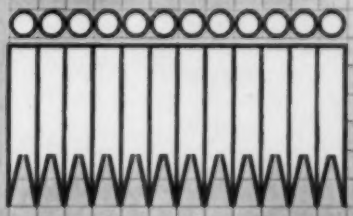

1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

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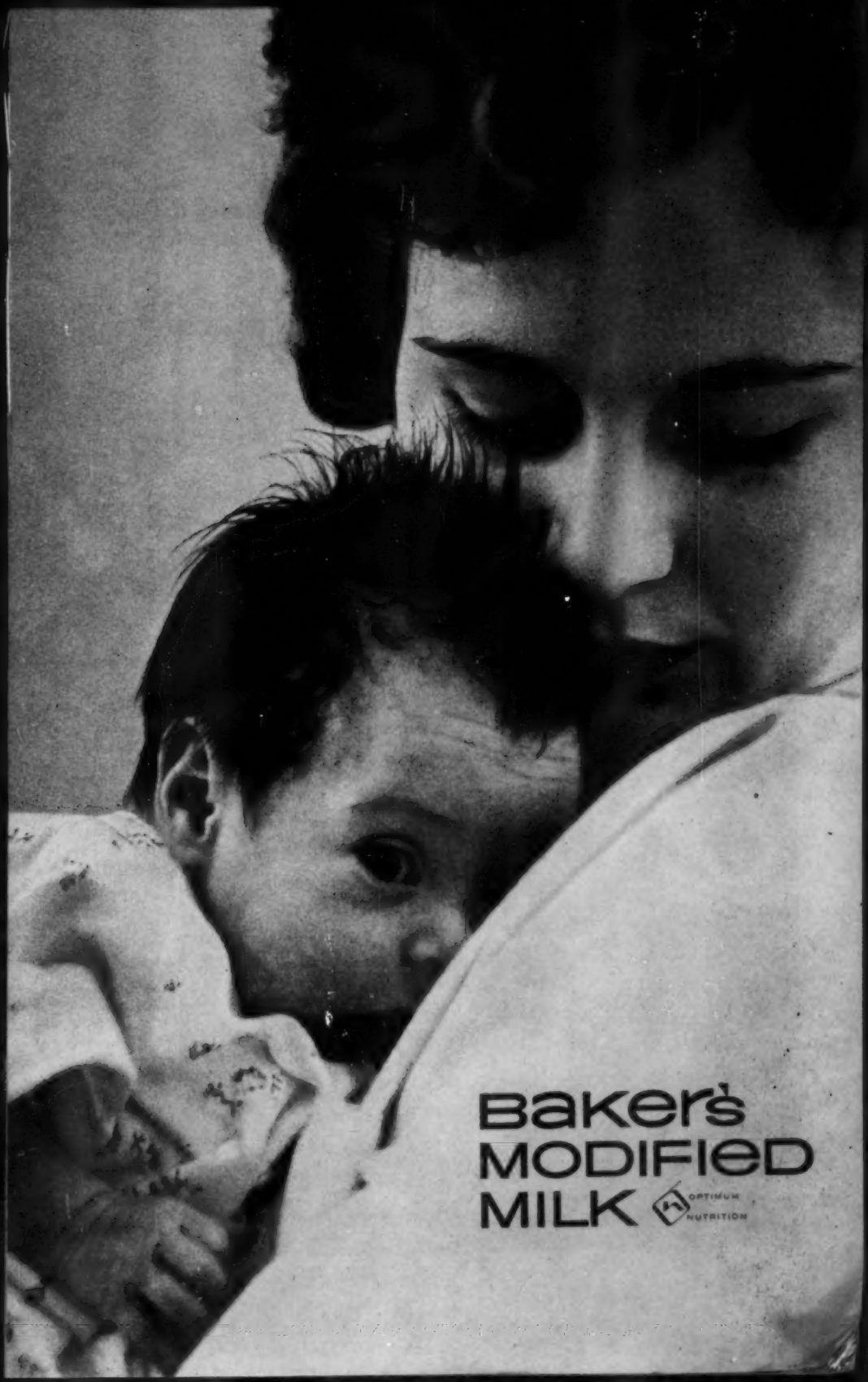
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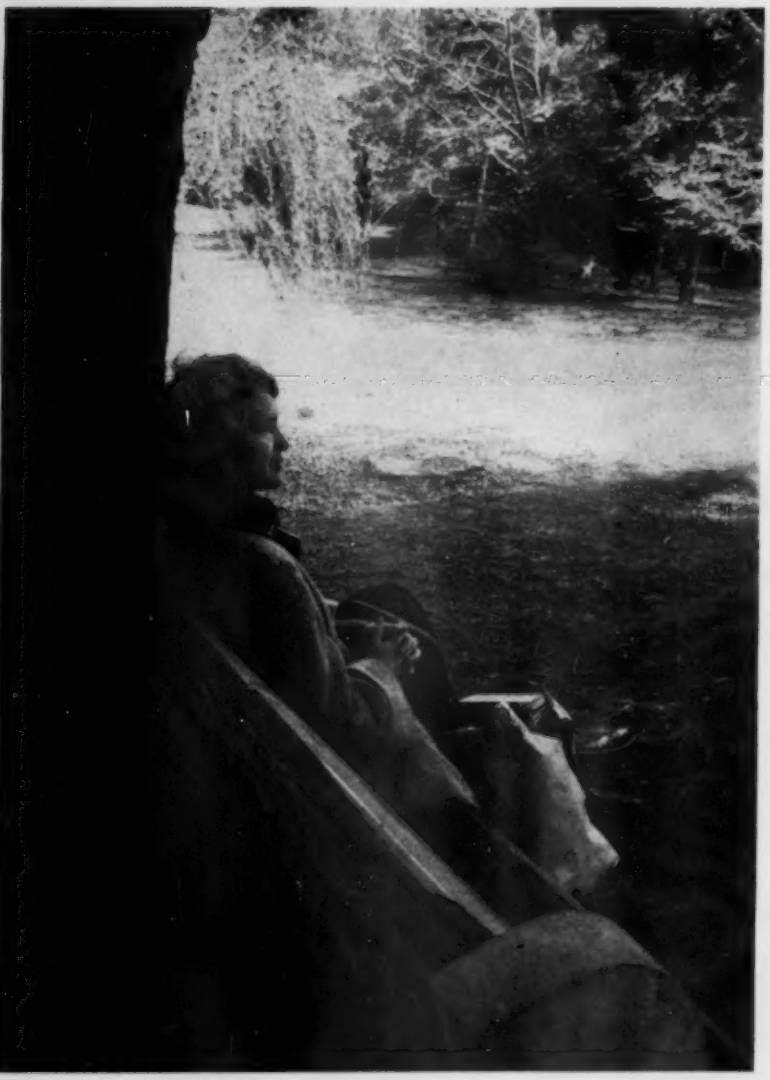

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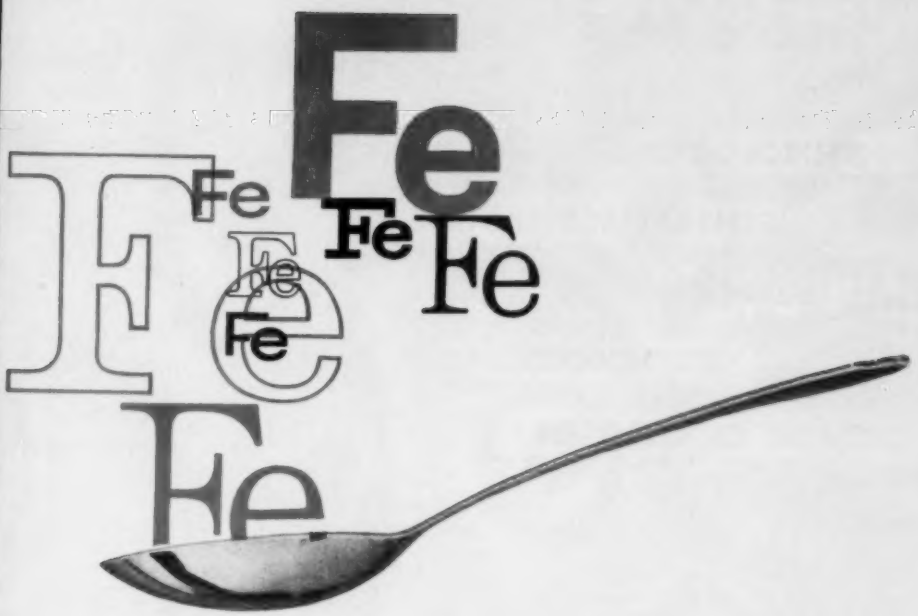

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Presentation of the John Howland Medal and Award of the American Pediatric Society to Dr. Daniel C. Darrow

At the Sixty-Ninth Annual Meeting, May 7, 1959, Buck Hill Falls, Pa.

INTRODUCTION AND PRESENTATION BY DR. HERBERT C. MILLER

Dr. Stokes, Members of the American Pediatric Society and Guests:

You will recall that two years ago this Society deviated from its usual custom and held its annual meeting in June instead of May. This change coincided with a curious phenomenon in our schools and colleges. Instead of listening to the customary platitudes and exhortations from commencement speakers, the graduating classes that year were treated to a refreshing change. Commencement orators almost to a man joined spontaneously in an attack against "The Organization Man" and "The Man in the Gray Flannel Suit." The American Pediatric Society with its usual foresight anticipated this national outburst by electing to its presidency in the preceding year the one member who more than any other is the living embodiment of the nonorganization man. He has never to my knowledge owned a gray flannel suit. Quite the contrary. He occupied the presidential chair that June in Carmel bedecked in a brilliant, red flannel shirt, sans coat and sans tie. Although world famous for his intellectual achievements, he has never been above secretly enjoying the startled looks on the faces of friends at his off-beat, colorful appearance or at one of his outlandish witticisms. He would have us think that the beret bought in France in 1950 was just to keep his head warm, and the Volkswagen bought in Germany in 1954 was just to save money, but there are some who suspect that he also enjoys them as badges of his freedom and independence. Let there be no mistake about this freedom and independence. It is not the desire to be different for the sake of being different, but is the kind of freedom, the lack of which, according to Archibald MacLeish, is the real crisis in the life of our Society. MacLeish states that the lack of this freedom "permits knowledge of the heart to be divorced from knowledge of the head and allows us to acquiesce in someone else's knowing and hence in someone else's deciding."[1] This lack does not exist in Dr. Darrow.

The roots of his freedom of thought and action can readily be traced. I am indebted to his brother, Dr. Kent Darrow, for the following description of family life and his childhood years in Fargo, N. D.:

Dan was born in 1895, the youngest of five children, to a pioneer surgeon and a mother very active in all civic works. She was on the school board a number of years, was the head of the

Submitted for publication June 30, 1959.

From Children's Mercy Hospital and the Department of Pediatrics, University of Kansas School of Medicine, Kansas City.

suffrage movement in North Dakota and was active in the national movement.

Dan grew up a normal boy, active in all the usual boy's activities. He was a very good basketball player and hunted the upland game and ducks, as his older brothers did. When his mother campaigned for suffrage in North Dakota, Dan was about fourteen or fifteen years old. He was her chauffeur on these campaigns. Once, when someone in the crowd shouted that she should go home and rock her baby, Dan spoke up and said, "I'm the baby and I don't like to be rocked."

Mother did most of the raising of the children and she influenced our thoughts and life even more than our father. His influence was by the example of a life dedicated to his patients and the whole community. Father was a true pioneer surgeon. He had a little more education than most medical students of his day. He graduated from high school, had one year of college at Lawrence, Wisconsin and graduated from Rush Medical College in 1878. He grew up with the modern development of surgery and was a finished surgeon when he died in 1919. Father was much more than the modern surgeon of today. He was a great diagnostician, psychiatrist and all-around physician. He was a great reader in all fields. The example of his life could not help but be an inspiration to all of us. The influence of mother and father on us was mainly by example and careful guidance and never by direct suggestion. No pressure was ever put on any member of our family to do any particular thing.

Dan's decision to take his last two years of college at Cornell University was his own idea and I don't know the reason. At the time he said he didn't expect to take up medicine. He even said he would make a good preacher if his home influence hadn't been so bad. He probably went to Hopkins because two of his brothers went there. Father knew that Hopkins stood out above the other medical schools at that time, something I did not realize until I had been there a while.

To give you a little insight into the freedom that was allowed in our family and the responsibilities we took, take the following example. My parents went abroad in the spring of 1910, my first year at Hopkins. They stopped off in Baltimore and I suggested to them that I could just as well go to Germany for the last trimester, as I had all the chemistry that was required. They approved and my roommate and I went to Strassburg and got a full semester in place of a trimester. My mother and father were still abroad in June when school let out at home. My married sister, Mary, who is eight years older than I, conceived the bright idea of sending my two younger brothers, Dan and Frank, over to me in Strassburg. She couldn't get in touch with the folks, so she just got some money from mother's bank account and sent the boys off. Dan was just past fifteen and Frank not quite eighteen. They arrived in Strassburg after the usual sightseeing trip up the Rhine. I sent the two boys on a bicycle trip through Switzerland. Dan tired out by the time they got to Bern, so the boys planned to go by stages, Frank on his bicycle and Dan by train, meeting at each stop and seeing the sights. Dan missed the first stop. He had asked the conductor to let him know when they got to Freiburg. The conductor told Dan the next stop was Freiburg. Dan, however, wanted to be sure, so he read the sign in the well-marked station and it didn't say Freiburg. He stayed on the train. When the conductor came along and saw him, he asked why he had not got off. Dan said the sign didn't say Freiburg, but said Sortie, so he stayed on. Frank met him by chance five days later in Geneva. Dan had made all the stops, seen all the sights and would have been back in Strassburg in time. The three of us were separated again between Strassburg and Munich. Dan was alone again for four or five days and didn't miss a thing.

Darrow entered The Johns Hopkins Medical School in 1916. The faculty had no difficulty in persuading him that the main purpose of that medical school was the study of health and disease. The research virus infected him early in his career. He was one of a small group of second-year students selected by Dr. MacCallum, Professor of Pathology, to help with some special research involving the administration of HCl to dogs. This investigation led to no immediately important gains in knowledge, but it launched Dr. Darrow on a relatively uncharted ocean. He has since become one of its first admirals. During this maiden voyage he learned how to determine carbon dioxide content of blood. A year or so later, probably inspired by the current interest in rickets, he attempted to set up a colorimetric method for determining phosphorus in blood. This venture proved unsuccessful. Upon graduation he accepted an instructorship in pathology with MacCallum, who had been so kind to him. But pathology was not his dish. He wanted to get into clinical medicine. The choice seems natural enough. The problems to be solved were legion. Clinical investigation in biochemistry was

beginning to make substantial progress. Darrow was well suited for the task, having been better grounded in chemistry and physics than most students even before entering Hopkins. He looked around for an opening either in internal medicine or in pediatrics and decided upon the latter, because an opportunity to intern at New Haven Hospital was offered him and because Ashley Weech told him that Dr. Park and Dr. Powers were such fine men. A succession of opportunities in pediatrics followed this one, and for the next several years he became quite mobile. He had a residency in pediatrics under Dr. Thomas Buckman at the Boston City Hospital. Buckman was a brilliant pediatrician with many excellent ideas on clinical problems to be investigated. One of them was to measure total electrolyte concentration of blood by determining its freezing point. Darrow assembled and built the necessary apparatus, and the two embarked on a fruitful, clinical study of dehydration.

Following his residency, he spent three years in St. Louis with Marriot and Hartman. Again, he found a salubrious climate for his interests with ample encouragement and assistance from both of these outstanding investigators. Dr. Jean Valjean Cook was another of the St. Louis group admired by Dr. Darrow, and very likely it was from Cook that he brought to New Haven his concept of streptococcal disease. While salt and water have been his chief interest, Dr. Darrow is well known to his intimates for his insight into and pungent comments on many diseases and aspects of medicine, including psychiatry. These comments usually have been unexpectedly and informally made on ward rounds, at table, or wherever two or three have been gathered together. These random thoughts have formed for the house officers, the younger members of the staff, and for many persons in this audience the most effective as well as the most delightful teaching. Lecturing, either formally or informally, has not been one of Dr. Darrow's favorite methods of communication.

As an undergraduate at Cornell, Dr. Darrow was a science major. He took advanced courses in chemistry and physics, as well as embryology, histology, and comparative anatomy—enough to have worried any medical school admissions committee concerning the breadth of his cultural interests. However, they need not have worried. He has truly been his father's son and has maintained a considerable interest in his fellow men, past and present. He has read widely in history, philosophy, politics, and science. His reading interests had something to do with meeting his future wife, Louise de Schweinitz. He was an instructor in pathology at Hopkins when she was a second-year medical student. I have it on the very best authority that superficially he did not appear to differ from the other instructors in pathology except in one respect. He was the only one attending classes with a copy of *The New Republic* in the pocket of his laboratory coat. He has always been an independent, do-it-yourself investigator and an independent political and social thinker, making him an independent voter, usually well to the left of center. He has combined a strong sympathy for the underdog in all walks of life with a considerable capacity for reducing overbearing feelings of self-importance among would-be top dogs. I remember as a student he was the most feared examiner of medical students on the clinical faculty. Woe unto the bright student sounding off without all the facts. The less gifted student often has had without knowing it a sympathetic supporter in Dr. Darrow, particularly in those faculty conclaves where an individual's fate is usually decided. Dr. Darrow has never been militant about his political and social beliefs. Possibly his sympathy for the pacifism of the Quaker Brethren precluded his becoming so. I have known him to go to unusual lengths to avoid an open conflict, but never to abandon his principles or to "acquiesce in someone else's deciding."

In 1928 Darrow returned to Yale and continued for the next 25 years his studies of body salt and water. He not only worked on salt and water, but he also played in it, salty or not. He brought the same enthusiasm to his play as to his work. Although he is not a master fly-caster, he bows to no one in his enjoyment of trout fishing whether the fish cooperate or not. I have seen him exhibit the same great pleasure over someone else's beautiful catch on the trout stream as when one of his young men has solved some knotty problem in the laboratory. While Connecticut offered him rich opportunities in fishing and sailing, Kansas has done better. He used to sail around on Long Island Sound, but in Kansas he has taken to racing. Along with other sailing enthusiasts he drags his Snipe sail boat behind his car to the races at Omaha, Wichita, and other distant points. Although he is not a frequent winner, his enthusiasm for the sport has won him the position of Commodore of one of the local yacht clubs in Kansas City. I think his pleasure in the out-of-doors is reflected by a passage he often quotes from Thoreau's "Walden":

> Go fish and hunt far and wide day by day—farther and wider—and rest thee by many brooks and hearthsides without misgiving. Remember the Creator in the days of thy youth. Rise free from care before the dawn and seek adventures. Let the noon find thee by other lakes, and the night overtake thee everywhere at home. There are no larger fields than these, no worthier games than may here be played. Grow wild according to thy nature, like these sedges and brakes, which will never become English hay. Let the thunder rumble, what if it threaten ruin to farmers' crops? That is not its errand to thee. Take shelter under the cloud, while they flee to carts and sheds. Let not to get a living be thy trade, but thy sport. Enjoy the land but own it not. Through want of enterprise and faith men are where they are, buying and selling, and spending their lives like serfs.

Research for Dr. Darrow never seemed to be drudgery no matter how hard the problem. He rarely gave the impression of working hard at it. Usually one could find him at his desk mulling over figures with a slide rule in hand, but always ready to drop even this activity to engage in argument, talk shop, or just talk. The appearance of ease has always predominated. Oftentimes the scientific arguments with Yannet, Harrison, Crismon, Pratt, Cook, Cheek, and others would last all morning or afternoon. Some one of them would come to him with an idea for investigation and usually be told it wouldn't work. Then would begin the defense of the proposition, which might go on for hours or even days. No one was ever dissuaded from carrying out his pet study, but a great many mistakes were avoided by this intensive preliminary argument. His own studies were so well thought out ahead of time that the actual laboratory procedures appeared only to confirm what he already knew before he started. He has always done a large share of the laboratory work himself and encouraged everyone else to do the same. He argued very wisely that this was the one way to recognize errors before it was too late. He has never hesitated to build whatever apparatus he needed, no matter how complicated, relying on his knowledge of physics and chemistry to carry him through. I remember one winter he built his own apparatus for measuring pH of the blood, because he didn't trust the commercial products then available. He has never been particularly interested in seeking outside financial support for his projects. It was a matter of satisfaction to him that his investigations cost perhaps not more than a thousand dollars a year for equipment, materials, and animals, and that good answers could be obtained without a super organization of people and money. He has never deigned to simplify the results of his research or thinking. The field of his endeavors is complex and requires hard work on the part of those who would attempt to cultivate it.

It is quite obvious as to why he is receiving the Howland Award today. He has done what Justice Oliver Wendell Holmes considered was "the best service that we can do for our country and for ourselves:

To see so far as one may and to feel the great forces that are behind every detail . . . to hammer out as compact and solid a piece of work as one can, to try to make it first rate, and to leave it unadvertised."

University of Kansas, Kansas City 3, Kan.

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The Significance of Body Size

ACCEPTANCE OF THE JOHN HOWLAND AWARD BY DR. DANIEL C. DARROW

For some time I have felt that doctors have created unnecessary confusion in the rules intended to take account of the different body sizes of infants, children, and adults. The difficulty arises largely from failure to utilize available knowledge of physiological relationships. Doctors know that total metabolism is considerably greater per kilogram of body weight in infants than in adults. Consequently, total metabolism rather than weight is the appropriate measure of those functions dependent on rate of metabolic turnover. Body weight is the measure of the mass of water, electrolyte, and protoplasm in which metabolic changes are taking place. In other words, body size has two dimensions. Attempts to bypass either of these dimensions fails to bring into view the relevant physiological relationships and establishes no adequate frame of reference which permits logical analysis. However, using the correct dimensions, present knowledge permits the same physiological principles to be applied to many problems involving infants, children, and adults. When change in body size is involved, the significance of both total metabolism and weight must be considered.

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Certain Functions Related to Metabolic Rate

Certain physiological functions which are related to total metabolism are shown in Table 1. Everyone recognizes that the primary function of food is to meet energy expenditure. Despite this fact, protein requirements are usually stated in terms of body weight with factors which differ with age. Nevertheless, food contains essentially the same proportions of total calories as protein, fat, and carbohydrate at all ages. At the lower limit, infants thrive on human milk providing about 8% of the calories as protein. Adults remain healthy on an equally low proportion of total calories as proteins of excellent nutritional quality, if caloric intake is sufficient. The table shows the usual proportion of calories as protein, fat, and carbohydrate. Considerable variation from these proportions is satisfactory. There is no convincing evidence that diets containing more than 20% of the calories as protein are advantageous in undernutrition when total calories are sufficient. Fat

Table 1

CERTAIN FACTORS RELATED TO TOTAL CALORIES

FOOD : TOTAL CALORIES	= 12% P + 38% F + 50% CHO	
CIRCULATION : O_2 ÷ AV DIFFERENCE	= 0.22 ÷ 0.05	= 4.5 L/CAL.
WATER EXPENDITURE	– ABOUT 150 ML / 100 CAL.	
LUNGS	13 ML. X 5	IN HYPERPNEA
SKIN	30 ML.	WITH NO SWEAT
SWEAT	VARIABLE	TO REGULATE HEAT BALANCE
URINE	V = OSM ÷ [OSM]	= 40 ÷ 100 TO 1400
		= 25 ÷ 100 TO 1400
STOOLS	0 TO 10	NO DIARRHEA

and carbohydrate calories are apparently interchangeable, provided a minimum of each is given. Thus diets at all ages meet nutritional requirements when calorie expenditure is satisfied with appropriate proportions of the calories as protein, fat, and carbohydrate. Since water expenditure is also related to total metabolism, the caloric concentration of infant's food, or mixtures which are gavaged should be essentially the ones used for infant feeding. This fact has not always been appreciated by physicians attempting to give high calorie foods by gavage.

It is generally accepted that normal expenditure of water is related to total metabolism. Nevertheless, this principle is seldom taught in adult medicine. Furthermore, many doctors do not understand how simply the physiological principles determining normal expenditure of water may be used to predict the normal variations in water loss. The loss from the lungs is about 13 gm. per 100 calories metabolized but may increase fivefold with hyperpnea. Without sweating, about 30 gm. of water per 100 calories metabolized diffuses through the skin. Accordingly, insensible water loss may be as little as 43 gm. per 100 calories. Since usually a small amount of sweat is formed, 60 gm. is a better figure for the usual hospital patient.

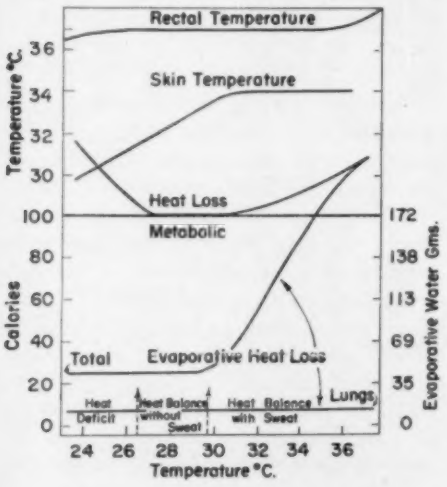

Figure 1

In response to the necessity for dissipation of heat, sweat may increase water loss from the skin from 30 to quite high figures. Figure 1 shows the evaporative water and heat losses from the skin at varying environmental temperatures in a quiet nude subject. The diagram is based on data of DuBois.[1] Below 80 F, body temperature decreases until a chill develops. Between 80 and 84 F variations in skin circulation permit regulation of body temperature without sweat formation. Above 84 F heat balance is attained by evaporation of sweat. Above 94 F all heat loss is attained by evaporation of water. The figure shows that evaporative water loss is about 100 gm. per 100 calories at 94 F. The evidence indicates that essentially the same rules for loss of water from the lungs and skin apply at all ages when related to total metabolism and environmental conditions. The losses from the lungs and skin are obligatory in all patients.

The kidneys are required to excrete essentially the same load per unit of metabolism at all ages. Urine volume equals load divided by concentration. The load of the usual diet is about 40 mOsm per 100 calories, while the load is about 25 mOsm per 100 calories during parenteral fluid therapy. The lower limit of concentration is about 100 mOsm per liter of urine while the upper limit is 1,400. Consequently, the appropriate urine volume is readily calculated from the load estimated from total metabolism. It is desirable to prescribe fluid intakes leading to urinary concentration between 300 and 400 mOsm per liter because this is the concentration excreted by kidneys unable to vary urinary concentration and is also the one permitting normal kidneys to save water by forming a concentrated urine or excrete water in a dilute urine. Consideration of urine volume in terms of load related to calorie production enables one readily to calculate the appropriate urine volume. The relationship

is simple to remember and applicable at all ages.

The blood circulation is also directly related to total metabolism. One calorie is produced by the consumption of 0.22 liter of oxygen. Considering the average arteriovenous oxygen differences as 0.05 liter of oxygen per liter of blood, the average circulation is about 4.5 liters per calorie. This is close to the basal rate per minute in an adult. However, average venous blood represents a mixture arising from tissues extracting a larger or smaller proportion of oxygen. Consequently, the circulation rate must provide sufficient oxygen to the most vulnerable tissue. The relation of circulation to calories readily explains why the circulation must be rapid in anemia and why high output failure is likely to result from fever. It also explains why patients with right-to-left shunts require high rates of circulation unless hemoglobin concentration is high. The relation of circulation to metabolism indicates that patients with more or less normal circulation are able to handle the amounts of fluid required in parenteral therapy. It is not necessary to use separate rules for rates of injection provided the fluids do not deviate greatly from the requirement indicated by total metabolism for the period of injection.

Shock produces permanent damage when diminished rate of circulation fails to meet metabolic needs of certain tissues. In this respect the brain is the most susceptible to anoxic injury. Indeed, one can consider that the acceleration of brain metabolism accompanying high fever produces cerebral injury in part as a sort of localized anoxic injury occurring when other tissues are not in serious danger. The liver is probably the next most susceptible, owing to the fact that normally about two-thirds of the oxygen comes from the portal circulation. Because vasoconstriction limits renal circulation in shock, the kidneys may suffer permanent damage when recovery from the acute circulatory disturbance may follow. It is these concepts that make prompt treatment of shock essential. In addition, they point out the importance of reducing caloric expenditure and providing adequate hemoglobin concentration as well as blood volume.

As has been pointed out by Crawford and associates,[2] drug dosage is more likely to be related to total metabolism than body weight. This conclusion is justified to the extent that the concentration of a drug is determined by the dose and the rate of excretion or rate of metabolic alteration of the drug in the body. Nevertheless, the dose of drugs excreted or metabolized slowly may follow weight rather than total metabolism. Drug dosage obviously involves other factors, but both weight and metabolic turnover may have to be considered.

Because the skin regulates heat loss, the area of the skin sets certain limits to dissipation of heat in warm-blooded animals. This fact underlies Rubner's hypothesis. Subsequent studies have indicated that surface area does not agree as closely with heat production as was originally claimed and surface area is known not to predict total metabolism of both large and small animals. Nevertheless, surface area is the best measure of basal metabolism in adults. About 1,000 calories per square meter is a reasonably satisfactory prediction of the metabolism for 24 hours of fasting, resting patients at all ages, except that serious objections can be raised for infants.[3] In the newborn period, surface area is quite erroneous. It is clear that surface area for subjects of the same weight is superior to the values predicted from weight alone. However, the prediction of the same metabolism per square meter is not superior to weight tables for subjects of widely different weights. It is more accurate as well as more convenient to use a table relating weight to metabolism in pediatrics. Table 2 is satisfactory. In any case, corrections should be used for alterations in metabolism by fasting, fever, and activity. Because the error of prediction is likely to be 15% by any system, precise refinements are not

Table 2

CALORIES EXPENDED IN 24 HOURS DURING FASTING

Weight Kg.	Calories/Kg.
Newborn	45 - 50
3 - 10	60 - 80
10 - 15	50 - 65
15 - 25	40 - 50
25 - 35	35 - 40
35 - 60	30 - 35
Over 60	25 - 30

justifiable. I believe the final calculations should be in terms of calories in order not to obscure the physiological relationships which we are postulating.

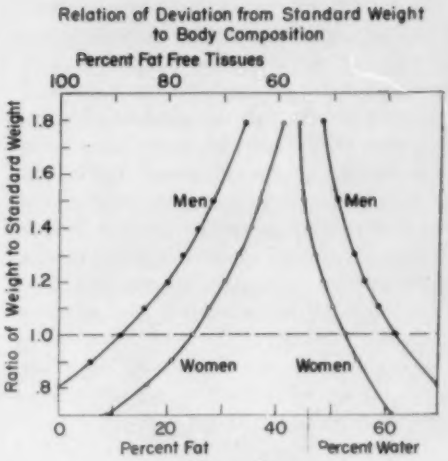

Figure 2

Significance of Body Weight

Body weight includes the metabolically active tissues, the supporting structures and fat serving as a reserve source of energy. The water occurs in both extracellular and cellular structures which have different contents of electrolytes. Since the proportions vary with nutritional status, sex, and age, body composition is not revealed by weight alone. For this reason, it is important to recognize the probable variations in composition of 1 kg. of tissues.

Moulton[4] showed that mature animals have a lean body mass of relatively constant composition. In mature humans, the fat-free tissues are about 71% water and 29% fat-free solids. Young men of ideal weight have about 12% fat and young women 23%. Keys and colleagues[5] found that changes in body weight of normal adults did not result from changes of pure fat but a mixture containing about 60% fat, 33% water, and 7% solids. Measurements of thiocyanate space indicate that most of the water is extracellular. Figure 2 relates changes in body weight of normal subjects to additions or subtractions of deposit fat of the composition suggested by Brozek and Keys. The deviation in weight may be expressed as the ratio of actual weight to the ideal weight for height. The chart shows the predicted changes in body water, fat, and lean body mass. According to the chart, normal men can lose only 20% of

Table 3

COMPOSITION OF 1 kg. OF TISSUES OF INFANT AND WOMAN

	Solids gm.	H_2O gm.	N gm.	Cl gm.	Na mM.	K mM.	Ca mM.	Mg mM.	P mM.
INFANT									
GROUP I	74	374	8.5	33	50	74	207	4.9	118
GROUP II	84	386	11.3	18	23	38	0.8	2.2	32
CARCASS	155	755	19.7	52	75	43	208	7.5	165
ADULT									
GROUP I	96	180	9.6	18	42	79	472	10.4	260
GROUP II	108	380	14.3	13	18	456	1.9	3.1	35
CARCASS	204	560	23.0		74	560	474	13.4	318

FAT OF INFANT 90 gm.; OF ADULT 236 gm.

body weight without involving a change in lean body mass. Women can lose a considerably greater proportion of body weight, owing to the greater normal fat content.

Figure 2 can only be used to illustrate the sort of changes in body composition that develop in normal young adults who deviate from ideal weight for height. The chart cannot be applied to children because normal fat content of children is not known, although the composition of the lean body mass may be approximately the same as in adults. Owing to the wide variation in the composition of lean body mass and total fat of infants, it is unlikely that a similar chart can ever be used for infants.

The wide difference in composition of 1 kg. of tissue of a newborn infant and that of an adult woman aged 41 years is shown in Table 3. Group I represents the contribution of the sum of bones, skin, lungs, plasma, fat, and connective tissue, while Group II is the sum of muscle, liver, heart, brain, kidneys, erythrocytes, and intestines. The former are predominantly extracellular and the latter, intracellular. The sum of Groups I and II derived from separate tissue analyses agrees satisfactorily with the content of the body. The value for the body Na of the adult is regarded as probably too high. The infant shows greater water explained by lower fat and fat-free solids; the higher chloride value of the infant indicates a considerably greater extracellular volum. The adult contains about the same Na and more Ca and P, owing to denser calcification of bones.

The similarities and differences in composition are better illustrated by calculating the same data per 100 gm. of fat-free, bone-salt-free solids (Table 4). These constituents are excluded because they contribute little or no water and electrolyte dissolved in body water. The table shows about the same nitrogen, potassium, magnesium, and phosphate. Intracellular composition of the newborn infant probably does not differ greatly from that of adults. On the other hand, extracellular water accounts for a water content a little over one and a half times as great per 100 gm. of fat-free, bone-salt-free solids. This conclusion is indicated by the greater Cl and non-bone Na of the infant. Since the proportion of solids in the tissues of Group I is about the same in the infant and the adult, solids such as collagen are not increased in the infant. Consequently, the increased extracellular fluids of infants apparently resemble an ultrafiltrate of plasma. It can be estimated that extracellular fluids are over 40% of the body weight in the infant and only 20% in the adult. Owing to the absence of pitting edema, extracellular fluid of infants probably exists as a gel. The gel restricts movement of fluids under pressure. The studies of undernourished infants in Mexico City[6] show increased

Table 4

Body Composition per 100 Gm. of Solids Excluding Fats and Bone Salts

	Solids	H_2O	N	Cl	Na	K	Mg	P
			Infant					
Group I	39	273	6.2	24	26	5	—	—
Group II	61	282	8.3	13	17	28	16	23
Carcass	100	565	14.7	39	51	32	2.3	38
			Woman					
Group I	30	116	6.2	12	17	5	—	—
Group II	70	245	9.2	8	12	29	2	23
Carcass	100	362	14.8	—	38	36	2	35

extracellular fluids without pitting edema. It is probable that absence of pitting does not exclude increase in extracellular fluids.

Cheek [7] and Forbes and colleagues [8] determined body chloride from the dilution of bromide. Data show the changes with growth. One may conclude that extracellular volume and body chloride decrease rapidly during the first year and approach adult proportions by the end of the second year. Part of the change is due to increase in deposit fat as is indicated by decrease in body water from 75% to 60%. Decrease in thiocyanate space confirms the conclusions based on bromide space.[9]

In abnormal states one may expect body composition to change owing to expansion or contraction of extracellular fluids. Deposit fat and fat-free solids decrease in undernutrition. Probably cell composition is relatively well preserved, though studies from Mexico City [6] showed striking increase in cell water and Na in relation to solids. Decrease in muscle potassium is well recognized as a part of a number of disturbances in body water and electrolyte that do not involve profound changes in cell structure. In order to keep the discussion within a tolerable length, I shall use the remaining time to point out the significance of changes in serum Na concentration in relation to body water and extracellular Na.

Despite the variations in proportion of extracellular fluids, the magnitude of deficits of Na and water are related to total water rather than extracellular volume. This conclusion may be deduced from the type of osmotic equilibrium maintained between extracellular and intracellular fluids.

Because cell membranes are freely permeable to water and the freezing points of serum and cells are essentially the same, the osmotic pressure of extracellular and intracellular fluids are equal. The following equations formulate this relationship:

$$\left(\frac{Osm_r + Osm_d}{W}\right)_e = \left(\frac{Osm_r + Osm_d}{W}\right)_i$$

$$\left(\frac{Osm_r}{W}\right)_e = \left(\frac{Osm_r}{W}\right)_i$$

Where subscripts r and d refer to restricted and diffusable osmols and subscripts e and i refer to extracellular and intracellular fluids. The second equation omits Osm_d because the diffusable osmols exist at the same concentration in all body fluids. The second equation may be modified to illustrate certain factors determining distribution of body water and serum Na concentration.

Because extracellular Na is the predominant extracellular cation and most of the anions are univalent, the restricted osmols of extracellular fluids are approximately $2(Na_e)$ and osmolar concentration twice the Na concentration in serum water or $2[Na]_s$.

$$2[Na]_s = \left(\frac{2Na}{W}\right)_e = \left(\frac{Osm_r}{W}\right)_i$$

$$2[Na]_s = \frac{2Na_e + (Osm_r)_i}{W_e + W_i}$$

The first equation shows that intracellular water varies inversely with serum Na concentration. This is the relationship demonstrated by Yannet and me [10,11] over 20 years ago. At this time we found evidence that the shifts of water in hyponatremia are not so great as the equation predicts. Recent studies by McDowell and colleagues [12] show that intracellular osmols probably decrease when hyponatremia develops and increase when hypernatremia develops. This finding does not invalidate the equation but indicates that intracellular osmols cannot be considered as strictly constant. The equation shows that serum Na concentration is altered by changes in intracellular osmols. For example, serum Na may rise owing to retention of K when the balance of Na and water does not explain the change.[13,14] The implications of this equation are more fully discussed elsewhere.[15]

Recognizing the uncertainty of precise interpretation of the second equation, simultaneous equations may be used to estimate the magnitude of change in water or Na required to produce a given change in serum Na concentration.

First, body water may be considered constant when a change in extracellular Na, ΔNa_e, develops. Considering normal

$[Na_e]$ as 140 and $W_e + W_i$ as W_t or total body water

$$2 \times 140 = \frac{2Na_e + (Osm_r)_i}{W_t}$$

$$2[Na]_s = \frac{2Na_e + \Delta Na_e + (Osm_r)_i}{W_t}$$

$$\Delta Na_e = ([Na]_s - 140)W_t$$

If $[Na]_s$ is 110 and W_t is 0.6, ΔNa_e is -18 mEq. per kilogram of body weight. Allowing for changes in intracellular osmols 15 mEq. per kilogram would be more nearly correct.

If body Na is constant and body water is changed by ΔW

$$2 \times 140 = \frac{2Na_e + (Osm_r)_i}{W_t}$$

$$2[Na]_s = \frac{2Na_e + (Osm_r)_i}{W_t + \Delta W}$$

$$\Delta W = \left(\frac{140 - 1}{Na_e}\right) W_t$$

If W_t is 0.6 per kilogram and $[Na]_s$ is 170, ΔW is -120 gm. per kilogram. Allowing for changes in intracellular osmols indicates that 100 gm. may be more nearly correct.

The equations cannot be used clinically except perhaps as a rough approximation when serum Na is very low and water deficit is likely to be negligible or when serum Na is very high and deficit of Na is likely to be negligible. The equations do indicate the probable maximal deficits of water and sodium. Alterations of serum sodium concentration are produced by essentially the same changes in sodium or water in infants and adults except for the differences accounted for by total water. The predicted alterations in serum sodium concentration are independent of extracellular volume. There may be limitations imposed by the fact that the proportionate decrease in extracellular volume is greater as the proportion of extracellular volume is less. Sodium concentration behaves as if sodium were present in total body water at the concentration in serum.

Usually water and sodium change concomitantly and in varying proportions. When extracellular water and sodium are lost at the concentration in serum, isotonic dehydration develops. I do not believe that we know the magnitude of isotonic loss of extracellular fluids resulting in marked symptoms. Yannet and I surmised that the loss was equivalent to about 80 ml. per kilogram in dogs. The losses of water were about 125 ml. and 9 mEq. of Na per kilogram in infantile diarrhea.[15] This is equivalent to about 80 ml. of extracellular fluid plus losses from the cells.

Recognizing the uncertainty of any estimates, Table 5 suggests the range of deficits of water, Na, Cl, and K per kilogram of body weight. For a given degree of dehydration, the estimation would vary with total water of the individual. Consequently the amounts would be greater per kilogram

Table 5

Estimated Deficits in Marked Dehydration per Kg. of Body Weight

	Hypotonic	Isotonic	Hypertonic
Water gm.	0-20	20-100	80-100
Na mEq.	10-15	4-8	0-4
Cl mEq.	8-12	3-6	+3-0
K mEq.	6-15	6-15	0-6

in infants than in children and adults. The larger figures are based on the assumption of greater deficits than those of the usual dehydration. Attention is directed to the fact that severe hypotonic dehydration may involve the loss of all the Na contained in 100 ml. of saline and but little water; hypertonic dehydration may involve the loss of 100 ml. of water and practically no Na. Severe isotonic dehydration is probably produced by loss of less than 100 ml. of extracellular fluid, but cell losses bring the deficit of water to 100 ml. per kilogram.

In general deficits of extracellular volume should be replaced fairly rapidly. In marked hypotonic dehydration it often is indicated to calculate the approximate deficit of sodium and administer about half of this amount as 3% NaCl. If the response is favorable, additional hypertonic salt solution may be given after a few hours. It is not considered advisable to inject rapidly the amount of glucose in water that will rapidly restore serum sodium concentration in hypertonic dehydration. Convulsions frequent-

ly occur when this practice is carried out and have been attributed to a process analogous to water intoxication produced by rapid lowering of normal serum sodium concentration by retention of water. Since Finberg [16] regularly finds anatomical lesion in the brain in hypernatremia, this may not be the correct explanation. Until better information is available hypertonic deficits should be considered as about one-fifth extracellular water and electrolytes and four-fifths glucose in water. The deficit fluid should be added to the amount indicated for normal and abnormal expenditure for 24 hours. The deficits of extracellular water and electrolytes can usually be replaced rapidly in isotonic dehydration, but there are advantages in starting to replace potassium deficits and expenditure early. Other factors remaining the same, extracellular fluids should be replaced with fluids containing Na and Cl in the same ratio as is found in extracellular fluids.

Potassium deficiency occurs in acidosis and alkalosis and may develop with normal, high, or low body water. The maximal deficiency is about 17 mEq. per kilogram and probably differs little in infants and adults because large deficits are more frequent in infants. The serum K concentration is an unreliable index of the state of intracellular potassium because serum concentration varies inversely with serum pH and other factors. It is clear that the rate of administration of K must be limited to the amounts which are unlikely to produce potassium intoxication. Consideration of the safe dose and the rate of retention indicates that severe depletion of potassium cannot be safely replaced in less than three to five days by parenteral fluids.

The rules for safe administration of K are first to restore all or part of the deficits of extracellular water and electrolytes so that the circulation is adequate and oliguria is overcome. There is evidence that potassium intoxication is more readily produced when serum sodium concentration is low. Also serum potassium is likely to be somewhat high as long as serious acidosis persists. The initial replacement of extracellular electrolytes seldom requires more than one or two hours. Administration of potassium is then started by adding appropriate amounts of KCl or KH_2PO_4 to fluids which replace the remaining deficits of water, Na, and Cl, and cover normal and abnormal expenditure during the first 24 hours. In general the total dose should be no greater than 3 mEq. per kilogram per 24 hours, although infants with K deficiency tolerate 3 to 5 mEq. per kilogram per 24 hours. The limitation in adults is indicated by the rule that the concentration of K in fluid injected intravenously should seldom, if ever, exceed 40 mEq. per liter. When this rule is followed large persons may receive less than 3 mEq. per kilogram per day.

In the past, a great deal of attention was paid to amounts of sodium bicarbonate which would restore serum bicarbonate in acidosis and, more recently, to ammonium chloride in alkalosis. It was recognized that sodium bicarbonate modified acid-base equilibrium by accepting protons, and ammonium chloride by donating protons. Indeed disturbances in acid-base equilibrium may be defined quantitatively in terms of the balance of hydrogen ions. Actually the hydrogen ion concentration in body water remains relatively constant because the buffers accept protons in acidosis and the buffers donate protons in alkalosis. The balance of hydrogen ions in acidosis is indicated by the excretion of hydrogen ions during recovery and the acceptance of protons by bicarbonate as protons are released from the buffers. Similarly recovery from alkalosis is accomplished by excretion of base and acceptance of protons by buffers.

The magnitude of the balance of hydrogen ions in metabolic acidosis is shown in Table 6. In the experiments, Pitts and colleagues [17] injected 10 ml. per kilogram of N HCL into nephrectomized dogs. The serum pH was reduced to less than 7.0.

Table 6

ACCEPTANCE OF H^+ PER kg. OF BODY WEIGHT

	H^+
(1) BICARBONATE: $H^+ + Cl^- + B^+HCO_3^- \rightarrow B^+Cl^- + H_2CO_3\uparrow$	4
(2) BUFFERS: $H^+ + Cl^- + B^+Buf\,A^- \rightarrow B^+Cl^- + HBufA$	5
(3) RBC: $Cl_s^- \leftrightharpoons HCO_{3\,RBC}^- \rightarrow HCO_{3s}^- \leftrightharpoons Cl_{RBC}^-$	1
(4) BONES: $RCaCO_3Na + H^+A^- \rightarrow RCaA + Na^+HCO_3^-$	2-4

(1), (2) AND (3) FROM PITTS - ET. AL. IN DOGS RECEIVING 10 mM HCl.
(4) SUGGESTED BY BERGSTROM

About half of the hydrogen ions are accounted for by bicarbonate and the rest by buffers. The period of observation was short and the buffers were presumably intracellular for the most part. However, the data do not exclude participation by the bones. The table indicates the possible acceptance of hydrogen ions by bone carbonate. Bergstrom [18] estimated the possible acceptance of hydrogen ions as about the same per kilogram in infants and adults. The amount is over 15 mEq. per kilogram.

In addition to the above changes in the balances of hydrogen ions, the cells accept protons when deficiency of potassium develops. The reaction is illustrated for metabolic alkalosis with potassium deficiency [19] in Table 7. During recovery, about 2 Na^+ plus 1 H^+ leave the cells for each 3 mEq. of K^+ retained. Since the deficit of K may be 17, the excess of protons in the cells is equivalent to 5 mEq. of H^+. In metabolic acidosis with equal deficit of K, the retention of hydrogen ions, owing to this mechanism, is probably greater because less Na replaces the K deficiency in the cells.

The above brief outline of the role of the balance of hydrogen ions in disturbances of acid-base equilibrium indicates that the magnitude of the changes in hydrogen ion cannot be precisely estimated in patients. In metabolic alkalosis the excess of protons in the cells may exceed the deficit in extracellular fluids. Consequently restoration of serum bicarbonate concentration by administration of ammonium chloride is seldom, if ever, indicated. Potassium chloride not only restores the cell deficits of this ion but thereby releases hydrogen ions from the cells. Furthermore, potassium enables the kidneys effectively to excrete bicarbonate. In metabolic acidosis one cannot precisely know the magnitude of excess hydrogen ions in the body. If this were known, one would have to decide how much bicarbonate should be given as the potassium and sodium salts. The aim of therapy is not only to achieve normal acid-base equilibrium but normal body composition. It is safe to give 25 ml. per kilogram of ⅙ N sodium lactate in marked metabolic acidosis. However, too large amounts of sodium lactate are likely to produce meta-

Table 7

ACCEPTANCE OF H^+ WITH CHANGE IN CELL K

$$R^{=} + 3K^+ \rightleftharpoons 2Na^+ + 2Cl^- + H^+HCO_3^-$$

(CELL) $\uparrow\downarrow$ (EXTRACELLULAR)

$$RH^{=}2Na^+ \rightleftharpoons 3K^+\downarrow + 2Cl^- + HCO_3^-$$

FROM COOKE - ET. AL. IN RATS WITH METABOLIC ALKALOSIS

bolic alkalosis if potassium deficiency persists. Usually it suffices to treat metabolic acidosis with sodium and chloride in the ratio found in extracellular fluids, for example with lactated Ringer's injection. Fortunately precise correction of acid-base equilibrium is seldom necessary. Usually, the kidneys are able to restore acid-base equilibrium and body composition when deficits of extracellular electrolytes and water are replaced and sufficient water, Na, Cl, and K are available for the excretion of weak acids and bases. The physiological principles of fluid therapy are clear when deficits are calculated per kilogram of body weight in relation to serum concentrations, and normal expenditure is related to total metabolism and abnormal losses are considered in relation to the physiological disturbance.

The discussion has illustrated that variations in body size should be interpreted in terms of total metabolism and body weight. Only in this way are the relevant physiological relationships brought into view so that the same principles apply to infants, children, and adults. Problems involving rate of metabolic turnover are much the same per unit of metabolism, while problems involving concentration and volume are similar per unit of weight. I firmly believe that doctors are able to grasp the significance of these two dimensions of body size. With this knowledge, doctors can use the relationships applicable to all ages rather than a group of empirical rules not clearly related to physiological principles.

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Transactions of the American Pediatric Society

Sixty-Ninth Annual Meeting

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Buck Hill Falls, Pa., May 6-8, 1959

SCIENTIFIC PROGRAM

1. **Another Example of Bacterial-Viral Interaction: The "Cloud Baby," an Important Factor in the Transmission of Staphylococcal Infection in the Nursery and in the Home**

   Heinz F. Eichenwald, M.D.*; Olga Kotsevalov, M.D.,* and Lois A. Fasso, R.N.*

2. **An Attenuated Poliovirus Vaccine Trial in a Village Community**

   D. M. Horstmann, M.D.*; J. C. Niederman, M.D.*; J. R. Riordan,* and J. R. Paul, M.D.*

3. **"Viral" Infections of the Central Nervous System: Etiologic Studies of 713 Cases**

   Harry M. Meyer Jr., M.D.*; Capt. Richard T. Johnson (MC)*; Irving P. Crawford, M.D.*; Harry E. Dascomb, M.D.,* and Nancy G. Rogers, B.A.*

4. **Infectious Hepatitis: Control of the Disease, and Detection of Virus During Incubation Period and in Subclinical Infection**

   Saul Krugman, M.D.; Robert Ward, M.D.; John P. Giles, M.D.*; Oscar Bodansky, M.D.,* and A. Milton Jacobs, M.D.*

5. **Immunological Studies of a Non-polysaccharide Fraction of the Hemolytic Staphylococcus Aureus**

   Lt. Arthur Nunnery (MC) U. S. N.*; Mary Tinker, M.S.,* and William L. Bradford, M.D.

6. **Galactosemia: A Biochemical Study with Special Reference to the Genetic Mechanism and Mental Retardation**

   Kenneth Hugh-Jones, M.D., M.R.C.P.*; Alvah L. Newcomb, M.D.*; Irene Huang, Ph.D.,* and David Yi-Yung Hsia, M.D.*

7. **Observations on the Significance of Primaquine-Sensitive Erythrocytes in Patients with Congenital Nonspherocytic Hemolytic Anemia**

   William H. Zinkman, M.D.,* and Raymond E. Lenhard Jr.*

8. **Salt Restriction and Salt Load in Cystic Fibrosis of the Pancreas**

   Paul A. di Sant'Agnese, M.D., and Alfredo M. Vidaurreta, M.D.*

9. **The Incidence of the Female Sex Chromatin Pattern in Mentally Defective Males**

   H. David Mosier, M.D.,* and Lawrence W. Scott.*

10. **Relapse in Nephrosis Following Prolonged Remissions**

    Howard G. Worthen, M.D.*; Ida Gans, M.D.*; Robert L. Vernier, M.D.,* and Robert A. Good, Ph.D., M.D.

11. **Production of Nephrotic Syndrome in Rats by Sensitization to Rat Kidney Proteins**

* By invitation.

Walter Heymann, M.D.; Donald B. Hackel, M. D.,* and Janet L. P. Hunter, M.R.C.P., E.*

12. **Chorioretinitis and Central Nervous System Diseases in Infancy**
Richard J. Allen, M.D.,* and James L. Wilson, M.D.

13. **Relation of Intracellular Ions to Metabolite Sequences in Kwashiorkor**
Jack Metcoff, M.D.; Silvestre Frenk, M.D.,* and Irena Antonowicz, M.S.*

14. **The Effect of Potassium Supplementation of Wheat in the Diets of Infants**
Aree Valyasevi, M.D.*; Robert Kaye, M.D.,* and Lewis A. Barness, M.D.

15. **Histidine, an Essential Amino Acid for the Infant**
Selma E. Snyderman, M. D.*; Philip H. Prose, M.D.,* and L. Emmett Holt Jr., M.D.; with technical assistance of Ellen Roitman, A.B., A.M.,* and Audrey Boyer, B.S.*

16. **The Systolic Blood Pressure in Neonatal Asphyxia and the Respiratory Distress Syndrome**
Gerald Neligan, D.M.*

17. **The Response of the Newborn Baby to Inflation of the Lungs**
K. W. Cross, M.D.*; Marshall H. Klaus, M.D.*; William H. Tooley, M.D.,* and Kurt Weisser, M.D.*

18. **The Electrocardiogram in Children with Ventricular Septal Defect and Severe Pulmonary Hypertension: Correlation with Response of Pulmonary Arterial Pressure to Surgical Repair**
James W. DuShane, M.D.*; William H. Weidman, M.D.,* and Robert O. Brandenburg, M.D.*

19. **Evaluation of Pulmonary Vascular Bed in Infants and Children**
Forrest H. Adams, M.D.; I. Hunter Crittenden, M.D.,* and Harrison Latta, M.D.*

20. **Clinical Observations on Twenty Hydrocephalic Children Subjected to Ventriculoatrial Shunt**
David B. Shurtleff, M.D.,* and Eldon L. Foltz, M.D.*

21. **Correlation Between Intestinal Absorption and Mucosal Histology in Patients Apparently Recovered from Celiac Disease**
Charles U. Lowe, M.D.; Mary O. Cruise, M.D.*; Bernard Doray, M.D.*; Cyruis E. Rubin, M.D.,* and Lloyd L. Brandborg, M.D.*

22. **Testosterone-Induced Remission in Aplastic Anemia**
Nasrollah T. Shahidi, M.D.,* and Louis K. Diamond, M.D.

23. **Masculinization of Female Infant Associated with the Use of Stilbestrol During Pregnancy**
Alfred M. Bongiovanni, M.D.; Angelo M. Di George, M.D.,* and Melvin M. Grumbach, M.D.*

24. **An Experimental Approach to the Study of Adoption**
Julius B. Richmond, M.D.; Leonard Hersher, Ph.D.,* and A. Ulric Moore, Ph.D.*

25. **Teratogenesis: Embryonic Versus Placental Injury**
Robert L. Brent, M.D., Ph.D.*

26. **Thrombocytopenia and Intestinal Bleeding in Premature Infants**
Eugene Kaplan, M.D.

27. **The Significance of the Respiratory Distress Syndrome in Premature Infants**
William Allen Bauman, M.D.*

28. **The Use of Intramuscular Iron in the Prophylaxis of the Iron Deficiency of Prematurity**
S. L. Leikin, M.D.*

29. **Body Water in Relation to Nutrition of Permature Infants**
B. M. Kagen, M.D.; Natalia Felix-Balkcom, M.D.*; J. F. Turner,* and Joyce Jessamy, B.S.*

* By Invitation

30. **Acidosis in Premature Infants Created by Lactic Acid Milk**
Herbert I. Goldman, M.D.*; Norman B. Schell, M.D.*; Samuel Karelitz, M.D., and Eli Seifter, Ph.D.

31. **The Significance and Prevention of Iron Deficiency Anemia in the Premature Infant**
John A. James, M.B.,* and Mollie A. Combes, M.D.*

32. **Motions of the Pharynx and Larynx with Aeration of the Lung at Birth**
James F. Bosma, M.D., and John Lind, M.D.*

33. **Significance of the Infant's Cry**
Samuel Karelitz, M.D.; Ruth F. Karelitz, B.A., M.A.,* and Laura Rosenfield, B.A., M.A.*

34. **The Effect of Protein Intake on Renal Conservation of Water in Young Infants**
Henry L. Barnett, M.D.; Chester M. Edelmann Jr., M.D.,* and Vassiliki Troupkou, M.D.*

35. **Cerebrospinal Fluid Glutamic Oxalacetic Transaminase and Lactic Dehydrogenase Activity in Newborn Infants**
Miriam Lending, M.D.*; Lawrence B. Slobody, M.D.; Martin L. Stone, M.D.,* and Joan Mestern*

36. **Severe Neutropenia in a Newborn Infant with Shigella Alkalescens Sepis**
Joseph P. Rossi, M.D.,* and Ira K. Brandt, M.D.*

37. **Studies of Hemoglobins at Birth with Follow-Up Observations During Infancy**
Virginia Minnich, M.S.*; James K. Cordonnier, M.D.*; Barbara Jones, M.D.,* and W. Gene Klingberg, M.D.*

38. **Observations on Fetal and Newborn Bilirubin Metabolism**
William J. Waters, M.D.*

39. **Full-Term Newborn Infants Kept in the Prone or Supine Position in the Nursery: The Incidence of Crying, Diaper Rash, and Self-Inflicted Excoriations**
H. G. Keitel, M.D.*; R. Cohn,* and D. Harnish*

40. **Comparative Study of Human Milk and a Soya Bean Formula in Infant Nutrition**
Samuel J. Fomon, M.D.*

41. **The Treatment of Diarrhea Based on Fifty-Five Years of Private Practice**
Charles Hendee Smith, M. D.

42. **An Evaluation of Alkali Therapy in the Management of Salicylate Poisoning in Children**
Charles F. Whitten, M.D.*; Nirmala Kesaree, M.D.,* and Jesse F. Goodwin, Ph.D.*

43. **The Use of Surface Area and Homeostatic Capacities in Simplifying the Physician's Task in Prescribing Fluid, Food, and Drugs**
Allan M. Butler, M.D.; Nathan B. Talbot, M.D., and Robert H. Richie Jr., M.D.

44. **Magnesium Deficiency Complicating a Case of Severe Protracted Diarrhea**
H. David Mosier, M.D.*

45. **Hyponatremia in Severe Illness**
P. Rosenbaum, M.D.*; John L. Moore, M.D.,* and Marilyn C. Hughes, B.S.*

46. **The Effects of Low-Calcium Diet on the Management of the Severe Form of Hypercalcemia of Infancy**
F. X. Fellers, M.D.*; R. Schwartz, M.D.,* and E. B. D. Neuhauser, M.D.

47. **Early Versus Late Feeding of Infants of Diabetic Mothers: A Controlled Study**
A. J. Rudolph, M.B.*; J. P. Hubbell Jr. M.D.*; J. E. Drorbaugh, M.D.*; R. B. Cherry, M.A.*;

* By Invitation

P. A. M. Auld, M.D.,* and C. A. Smith, M.D.

48. **Enzyme Studies in Glycogen-Storage Disease (Hepatonephromegalic Type)**
Richard Wagner, M.D., and Rose Sparaco*

49. **Experiences with the Administration of Fat Intravenously**
S. A. Kaplan, M.D.*; J. Strauss, M.D.,* and A. M. Yuceoglu, M.D.*

50. **Influence of Diets High in Essential Fatty Acids on Lipid Patterns of Infants**
Julius Pomeranze, M.D.*; Alta Goalwin, M.D.,* and Lawrence B. Slobody, M.D.

51. **Blood Lipid and Protein Studies in Juvenile Diabetes Mellitus**
Howard S. Traisman, M.D.*; Alvah L. Newcomb, M.D.,* and Robert Hammes, M.D.*

52. **Hyperbilirubinemia in Infants of Diabetic Mothers**
P. M. Taylor, M.D.*; E. L. Birchard, M.D.*; N. H. Bright, M.D.*; J. H. Wolfson, M.D.,* and D. W. Watson, B.S.*

53. **Comparative Study of the Capacity of Various Commonly Used Solutions to Expand Blood Volume**
J. H. Probst, M.D.*; M. L. Terry, A.B.*; M. B. McIntire, R.N.,* and N. B. Talbot, M.D.

54. **The Occurrence of a Sex-Linked Coagulation Defect (P. T. C.) and an Autosomal Defect (S-Hemoglobin) in a Family and in a Single Individual**
Heyworth N. Sanford, M.D.; Gertrude Asrow, B.S.,* and Michael Limosani, M.D.*

55. **Congenital Deficiency of Factor VII Complicated by the Coagulation Defects of the Newborn Period**
S. Frederick Rabiner, M.D.*; Myron Winick, M.D.,* and Carl H. Smith, M.D.

56. **Serological Conflict Between Mother and Fetus**
Bela Schick, M.D., and Stephen Koveity, M.D.*

57. **Erythroblastosis Fetalis: Attempts at Prevention by Desensitization**
Fred H. Allen Jr., M.D.,* and Louis K. Diamond, M.D.

58. **Familial Pulmonary Fibrosis and Its Relationship with the Hamman-Rich Syndrome**
Bernard Laski, M.D., F.R.C.P. (C)*; W. L. Donohue, M.D.*; Irene Uchida, Ph.D.,* and J. D. Munn, M.D.*

59. **Hypoproteinemia and Edema as Early Manifestations of Fibrocystic Disease of the Pancreas**
Daniel S. Fleisher, M.D.*; Angelo M. DiGeorge, M.D.,* and Nancy N. Huang, M.D.*

60. **Hirsutism in Adolescent Girls—Possible Stein-Leventhal Syndrome: Report of Three Cases**
Alvin B. Hayles, M.D.*; Marilyn L. Cowger, M.D.*; Robert A. Salassa, M.D.*; Joseph Hyde Pratt, M.D.,* and Malcolm B. Dockerty, M.D.*

61. **Syndrome of Congenital Asymmetry (Hemihypertrophy), Shortness of Stature, and Elevated Gonadotropins**
Henry K. Silver, M.D.

62. **Cortisol Metabolism in the Newborn**
Robert A. Ulstrom, M.D.,* and Eleanor Colle, M.D.*

63. **Sexual Precocity and Pseudoprecocity in Girls**
Walter R. Eberlein, M.D.*; Alfred M. Bongiovanni, M.D., and Iris T. Jones, M.D.*

64. **Congenital Cretinism Associated with I^{131} Therapy of the Mother**
Esten W. Ray, M.D.*; Kenneth Sterling, M.D.,* and Lytt I. Gardner, M.D.

* By Invitation

65. **The Weltmann Reaction as a Screening Test for Detecting Abnormalities in Serum Proteins**
Susan C. Dees, M.D., and Jerome A. Grunt, Ph.D., and M.D.*

66. **The Significance of Serum Complement Levels for the Diagnosis and Prognosis of Acute and Subacute Glomerulonephritis**
Kurt Lange, M.D.*; Edward Wasserman, M.D.,* and Lawrence B. Slobody, M.D.

67. **Experimental Studies in Age-Conditioned Tolerance to Nephrotoxic Serum**
Philip L. Calcagno, M.D.*; Phatick K. Mukherji, M.D.*; Mitchell I. Rubin, M.D., and Kornel L. Terplan, M.D.*

68. **Experiences with Amphotericin B in Treatment of Histoplasmosis and Moniliasis**
Henry G. Cramblett, M.D.*; Hugh Moffet, M.D.,* and Samir Najjar, M.D.*

69. **Connective Tissue Studies in Rat Nephrosis: I. S^{35} Uptake**
James N. Etteldorf, M.D.; C. M. Johnson, M. D.*; George Brown, M.D.*; J. R. Teabeaut II, M.D.*; M. J. Sweeney, M.D.,* and C. B. Ferrell, M.A.*

70. **Connective Tissue Studies in Rat Nephrosis: II. Basement Membrane Metachromasia**
J. Robert Teabeaut II, M.D.*; James N. Etteldorf, M.D.; C. M. Johnson, M.D.*; M. J. Sweeney, M.D.,* and Carl B. Ferrell, M.A.*

71. **Antibiotics in the Treatment of β-Hemolytic Streptococcal Infections: Factors Influencing the Results**
Maxwell Stillerman, M.D.,* and Stanley H. Bernstein, M.D.*

72. **The Role of Staphylococci in Newborn Nurseries**
Katherine Sprunt, M.D.*

73. **Transmission of P^{32}-Labeled Candida Albicans to Newborn Mice at Birth**
Philip J. Kozinn, M.D.*; Claire L. Taschdjian, B.S.*; James Burchall, B.S.,* and Harry Wiener, M.D.*

74. **Fibrinous Bronchitis: Its Mechanism, Treatment, and Implications**
Vivian Tappan, M.D.*

75. **Chemoprophylaxis During Respiratory Infections in a Private Pediatric Practice**
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76. **Follow-Up Studies upon Infants with Coarctation of the Aorta and Patent Ductus Arteriosus**
M. R. Behrer, M.D.*; F. Peterson, M.D.,* and D. Goldring, M.D.*

77. **Congenital Dextrocardia: A Clinical, Roentgenologic, Electrocardiographic, Angiocardiographic, Catheterization, and Autopsy Study of Thirty-Six Cases**
Rene A. Arcilla, M.D.,* and Benjamin M. Gasul, M.D.*

78. **Ventricular Septal Defect: Indications and Contraindications for Surgery**
Catherine A. Neill, M.D.,* and Helen B. Taussig, M.D.

79. **Ventricular Septal Defect: Prognosis of Congestive Heart Failure in Infancy**
Beverly Morgan, M.D.*; Sylvia P. Griffiths, M.D.,* and Sidney Blumenthal, M.D.*

80. **Acid-Base Abnormalities Encountered with the Gibbon-Mayo Pump Using Blood Flow Rates of 2-2.4 Liters per Square Meter of Body Surface per Minute**
A. F. Hartmann Jr., M.D.*; A. Roos, M.D.,* and D. Goldring, M.D.

* By Invitation

81. **The Effect on the Child's Heart of Early Resumption of Normal Physical Activity Following Acute Rheumatic Fever as Evaluated Two to Fourteen Years Later**
Bessie L. Lendrum, M.D.*; Albert J. Simon, M.D.,* and Irving Mack, M.D.*

82. **Magnesium Kinetics in Muscular Dystrophy**
Leon Hellman, M.D.*; Barnett Zumoff, M.D.*; Abraham Kanof, M.D.,* and Benjamin Kramer, M.D.

83. **Febrile Seizures: Indications for Continuous Anticonvulsant Therapy and Observations on Prognosis**
J. Gordan Millichap, M.D.*; Jack A. Madsen, M.D.,* and Louis M. Aledort, B.S.*

84. **The Pediatric Management of the Muscular Dystrophic Child Based on Observations of Thirty Cases**
Lawrence T. Taft, M.D.*

85. **The Value of Cerebral Angiograms in the Diagnosis of Convulsive Disorders and Other Intracranial Lesions in Children**
Alfred Uihlein, M.D.,* and Haddow M. Keith, M.D.

86. **Pathogenesis of Paralysis in Hyperkalemic Familial Periodic Paralysis**
R. Klein, M.D.; T. Eagan, M.D.,* and Patricia W. Usher, M.S.*

87. **Treatment of Infantile Myoclonic Seizures with Corticotropin and a Corticosteroid**
June M. Dobbs, M.D.*; James D. Clements, M.D.,* and H. W. Baird, M.D.*

88. **Endocrine and Metabolic Observations in Children with Craniopharyngiomas Before and After Surgical Treatment**
John F. Crigler Jr., M.D.*; Donald D. Matson, M.D.,* and Ann E. Niall, M.D.

89. **Growth and Development of Negro Infants: Weight, Height, Pelvic Breadth, Head and Chest Circumference from Birth to One Year**
Roland B. Scott, M.D.; Althea D. Kessler, M.D.*; Bettie G. Clark, M.D.*; Howard H. Hiatt, A.B.,* and Angella D. Ferguson, M.D.

90. **Chronic Constipation in Childhood**
Giulio J. Barbero, M.D.*; Mary Brooks, A.B., M.A.*; Ih Chin Kim, M.D.,* and Marian G. Morris, B.S., M.S.W.*

91. **The Problem of Parental Criminal Neglect and Severe Physical Abuse of Children**
C. Henry Kempe, M.D., and Henry K. Silver, M.D.

92. **A Combined Study of Learning Disabilities in Children: A Progress Report on the Neurological and Physical Findings**
Paul R. Patterson, M.D.*; Ruth H. Solomon, M.A.*; Morton I. Weiser, Ph.D.*; Lenore Sportsman, M.D.*; Frederick D. McCandless, M.D.*; Dorothy Moyer, A.B.*; Phyllis R. Sands, M.S.*; Emily K. Kenfield, M.A.; Morris E. Eson, Ph.D.*; J. Roy Newton, Ed.D.*; Frederick Hesser, M.D.*; Stanley M. Ball, M.D.,* and Ruth Sheeran, M.S.*

93. **Attempts to Influence Phenylalanine Plasma Levels by Oral Feedings**
Harry Waisman, Ph.D., M.D., and Hwa L. Wang, Ph.D.*

94. **Long-Term Follow-Up of Children and Adults Exposed to Repeated Fluoroscopic Examinations (1920-1958)**
Ann McA. Birch, M.D., M.P.H.,* and David H. Baker, M.D.*

95. **Study of the Irradiation Protection Effect of Pooled Fetal Liver in Mice**

* By invitation.

John H. Githens, M.D.,* and Leone St. Vincent.*

96. **Tracheal Fenestration: A New Treatment for Chronic Pulmonary Disease**
E. E. Rockey, M.D.,* and Edward Wasserman, M.D.*

1. **Another Example of Bacterial-Viral Interaction: The "Cloud Baby," an Important Factor in the Transmission of Staphylococcal Infection in the Nursery and in the Home.** HEINZ F. EICHENWALD, M.D.*; OLGA KOTSEVALOV, M.D.,* and LOIS A. FASSO, R.N.* The Department of Pediatrics, The New York Hospital-Cornell Medical Center, New York. Introduced by S. Z. Levine, M.D.

Detailed studies on the spread of staphylococci in a number of different nurseries, carried out by the use epidemiologic technics in conjunction with air-sampling methods, have shown that a newborn infant infected with staphylococci may fall into one of two distinct groups. The majority of babies possess a low index of infectivity or contagiousness, while a small minority is highly infectious to others. Because infants of this latter group are literally surrounded by clouds of bacteria, they have been called "cloud babies."

Our evidence clearly indicates that these "cloud babies" are the major single factor responsible for explosive outbreaks of staphylococcal infection and disease, both during their stay in a nursery and, after discharge, within the family unit.

The factors that determine whether any given infant becomes a "cloud baby" or not have been investigated, using air-samplers to measure the degree of "cloudiness." The clinically well "cloud baby" contaminates the atmosphere chiefly from his respiratory tract, with skin, cord, or clothing representing only a minor source of microbes. The appearance of lesions of staphylococcal disease, such as impetigo, generally converts a noninfectious infant to a "cloud baby" and these sites of disease then contribute to the dissemination of microbes.

However, the majority of "cloud babies" do not present any overt sign of disease. Investigation of these clinically well, but infectious infants showed that a factor is responsible for the phenomenon of "cloudiness" which operates independently of the staphylococcus, is itself infectious, and has a distinct epidemiology of its own. This factor appears to consist of a number of different respiratory viruses commonly encountered in hospitalized newborn infants.

Thus, the "cloud baby" is in some respects similar to the premature infant with the "stuffy nose syndrome," but differs in that in the latter patient combined bacterial-viral infection results in the appearance of overt disease, while in the "cloud baby" this combination is not necessarily associated with illness, but rather promotes the spread of staphylococci.

2. **An Attenuated Poliovirus Vaccine Trial in a Village Community.** D. M. HORSTMAN, M.D.; J. C. NIEDERMAN, M.D.*; J. R. RIORDAN, and J. R. PAUL, M.D.* Section of Epidemiology and Preventive Medicine and Department of Pediatrics, Yale University School of Medicine, New Haven, Conn. Introduced by Nelson Ordway.

At the present time—largely due to the pioneering work of Koprowski and of Sabin—the use of oral attenuated poliovirus vaccines has reached the field trial stage. The present report concerns a small trial carried out in a semi-isolated Indian village community near Phoenix, Ariz., using the LSc strain of Type I poliovirus, kindly made available to us by Dr. Albert Sabin. The object of the trial was primarily to assess the effectiveness of the vaccine as an immunizing agent in young children in a population estimated to have a high degree of natural immunity. The study group included 21 Yaqui Indian families, in 6 of which a young child was fed attenuated

* By invitation.

poliovirus in a dose of 100,000 TCD_{50}. Specimens collected from as many of the 131 members of the group as possible included blood samples before the start of the trial and six weeks later, rectal swabs at three- to seven-day intervals for six weeks, beginning before attenuated poliovirus was introduced into the community, and fecal samples from the outdoor privies belonging to the study group families. In all, 163 blood specimens, 711 rectal swabs, and 302 privy samples were collected and tested. In addition, enterovirus activity in the general community was studied by examining 166 rectal swabs collected from children attending the Village Well-Baby Clinic, and by testing 237 collections of flies, trapped at 12 sites in the study area and peripherally. Tissue culture methods were used for all tests.

The results were as follows: 1. Only three of the six children fed virus became infected, and there was no spread of virus to any of the contacts, familial or extrafamilial. This is not surprising in view of the high degree of natural immunity in the study group as shown by neutralizing antibody determinations: only 10 of the 32 children under 5 lacked Type I poliovirus antibody at the beginning of the trial, and virtually all persons over 5 years possessed antibodies to all three types. 2. Many nonpoliomyelitis enteroviruses were found both in rectal swabs and privy samples including, in addition to untypable agents, ECHO 1, ECHO 5, ECHO 10, and Coxsackie B5. Their presence raised the question of interference as a mechanism which might block infection with attenuated poliovirus and thus curtail the efficiency of the oral vaccine. 3. Although there was little evidence of natural poliovirus infections in the children (a single Type III strain was isolated from a Well-Baby clinic child), the fly population of the area proved to be teeming with enteroviruses, including polioviruses Type I and III, which were isolated from 33 different fly collections.

The findings of this small trial bring out some of the problems of immunizing effectively against poliomyelitis with attenuated virus vaccine, particularly the possible competition from other enteroviruses in populations of this type.

Discussion

DR. AUGUSTA B. MCCOORD, Rochester, N. Y.: What is meant by the phrase, "Infection with poliovirus was produced in the children?"

DR. SAUL KRUGMAN, New York: In a recent study in association with Drs. Albert Sabin and Joan Giles we had an opportunity to feed attenuated polioviruses to a small group of 5- to 10-year-old children at the Willowbrook State School. Before receiving the attenuated polioviruses they were inoculated with four doses of Salk vaccine over a 14-month period. Either Type 1 or Type 3 attenuated poliovirus (depending on the type lacking prior to Salk vaccine immunization) was fed three months after the fourth injection of Salk vaccine. This study showed (1) that the immunity produced by the four doses of Salk vaccine had no effect on the amount or duration of virus excretion in the stools, and (2) that these immune children were capable of infecting other vaccinated children in the same ward where conditions were particularly suitable for fecal contamination. This study also showed that other enteric viruses (ECHO 9 and Coxsackie A) interfered with the multiplication of attenuated polioviruses.

DR. JOSEPH STOKES JR., Philadelphia: I asked Dr. Hodes to discuss this. He has done some very interesting studies and would like to show some slides to illustrate them.

DR. HORACE L. HODES, New York: Dr. Stokes asked me several weeks ago to comment on Dr. Horstmann's paper because some of the work that we have been doing has direct bearing on antibody immunity against polio and other viruses.

There are two points I should like to make. One is that the studies we have been carrying out are done by determining the presence of antibody by showing its blocking action against poliovirus. The antibody when it is present blocks the movement of the virus up a strip of filter paper. We have now had three years' experience with this filter-paper method.

The studies carried out in the last year, chiefly done by Dr. Ruth Berger in our laboratory, have shown very clearly that this method correlates quite well with the standard neutralization tests for determining the presence of polio antibody in the general population. We have reason to believe from recent experience that in the acute phase of poliomyelitis the blocking method may show anti-

body earlier in the course of infection than standard methods do. Or it may be that the filter-paper method shows an additional antibody which cannot be demonstrated by neutralization tests.

The following experience suggests these possibilities. Last summer in Winnipeg there were seven deaths from polio on Dr. Medovy's service in the Children's Hospital. These seven patients were autopsied and Type I poliovirus was obtained from all of them. Three of these patients died on the second or third day after the onset of polio, and their sera did not show antibody as determined by neutralization tests, the sera being obtained shortly before death. Dr. Medovy and Dr. Wilt who did this work gave us some of the sera of the three patients who died before neutralizing antibody appeared. We were able to show solid blocking antibody as determined by the filter-paper test.

This suggests the two possibilities I mentioned, either that this method is a much more sensitive one than the usual antibody test, or that there is an antibody, undetectable by neutralization tests, which may have an important role in immunity against poliomyelitis.

The second point I'd like to mention very briefly is that we have been able to label poliovirus with radioactive phosphorus, and by using Dr. Bill Hoyer's method of purifying a virus by passing it through a cellulose resin ion exchange column, we have been able to obtain radioactive purified virus. When this purified radioactive virus is used in the filter-paper test, it is possible to determine the presence or absence of antibody merely by counting the radioactivity of the strips of paper. By this means, tissue culture methods are eliminated.

The first slide illustrates some of our results.

There are shown two strips of paper. Each strip is 1.75 cm. wide and 18 cm. long. The strips of paper have been ruled off by pencil lines into 1 cm. spaces which are numbered 0 to 17. In this experiment, two sera were tested. One serum did not contain neutralizing antibody, the other did contain such antibody, as determined by standard tissue culture neutralization tests; 0.1 ml. of the serum which contained no neutralizing antibody was placed on Space 2 of the filter-paper strip shown on the left, while 0.1 ml. of the serum which did contain neutralizing antibody was placed on Space 2 of the filter-paper strip shown on the right. Each strip was then placed in a purified radioactive virus suspension, only the bottom half of Space 0 being immersed in the virus reservoir. Each reservoir contained purified radioactive virus which had a radioactivity of 2,400 counts per minute per milliliter. The titer of this virus was $10^8 TCD_{50}$ per milliliter. The strips were allowed to become wet through Space 17. They were then cut along the indicated pencil lines, and the radioactivity of each space was determined by counting in a gas-flow, thin-window counter. Presence of virus was determined by placing each space into a monkey-kidney tissue-culture tube. It will be seen that the radioactivity of the spaces of the strip on which had been placed serum which did not contain antibody is greater than that of corresponding spaces of the filter-paper strip on which had been placed serum which did contain neutralizing antibody. For example, Space 17 of the negative serum strip has radioactivity of 22 counts per minute, while the corresponding positive antibody paper strip has a radioactivity count of 2. Space 16 of the negative strip has a radioactivity of 21 counts per minute, while Space 16 of the antibody-positive strip has a radioactivity of 1 count per minute. Space 15 of the negative strip has a count of 15, while Space 15 of the positive antibody strip has a radioactivity count of 2, etc. Correspondingly, it will be seen that virus was present, as determined by tissue culture, on every space of the strip on which had been placed the serum which contained no neutralizing antibody. In contrast, all of the spaces beyond Space 9 of the filter-paper strip on which had been placed serum which did contain neutralizing antibody were negative for poliovirus. This shows good correlation between the spread of radioactive virus, as determined by radioactivity count and by actual determination by tissue culture of the presence or absence of virus on the various spaces of the filter paper.

The next slide shows a similar result with four filter-paper strips. The strip on the extreme left is one which has been treated with a serum which does not contain any antibody. It will be seen that the radioactivity counts on this paper are high throughout, being as follows: on Space 15, 85 counts per minute; on Space 16, 109 counts per minute; on Space 17, 92 counts per minute. All of these spaces contain virus, as shown by tissue culture. The next three strips of paper have been treated with sera which contain neutralizing antibody. The radioactivity of all three of these strips is much lower than that of the strip on which was placed serum containing no antibody. For example, on Strip 2, on which had been placed a serum of high neutralizing antibody titer, the radioactivity on Space 15 is 7 counts per minute; on Space 16, 4 counts per minute, and on Space 17, it is 0. No virus was found by tissue culture on any of the spaces of this strip of paper beyond Space 11. Similar results are obtained on the other two strips on which had been placed serum which contained neutralizing antibody.

I should like to ask Dr. Horstmann whether she has remaining serum obtained from the children during the first few days after they had been fed virus. We should very much like to determine

whether our paper strip method would show the presence of antibody. It is almost certain that standard neutralization tests for antibody would be negative.

DR. D. M. HORSTMANN: No early serum specimens were collected from the children in the Guadalupe Village Trial. However, we do have specimens from other children collected 7 and 10 days after virus feeding. Rarely were neutralizing antibodies detected on Day 7, but they were commonly present on Day 10. Possibly the "blocking antibody" of Dr. Hodes could be detected regularly on Day 7.

3. "Viral" Infections of the Central Nervous System: Etiologic Studies of 713 Cases. HARRY M. MEYER JR., M.D.,* CAPT. RICHARD T. JOHNSON (MC)*; IRVING P. CRAWFORD, M.D.*; HARRY E. DASCOMB, M.D.,* and NANCY G. ROGERS, B.A.* Department of Virus Diseases, Walter Reed Army Institute of Research, Washington, D. C. Introduced by Edward C. Curnen.

Acute infections of the central nervous system (CNS) of presumed viral etiology can generally be classified in one or another of three syndromes: aseptic meningitis, encephalitis, or "paralytic poliomyelitis." In 1953 Adair and co-workers, summarizing an 11-year experience at the Walter Reed Army Institute of Research, reported that of 854 cases of aseptic meningitis and encephalitis studied, approximately 25 were caused by mumps, lymphocytic choriomeningitis (LCM), and herpes simplex viruses and leptospiras.

The present report deals with etiologic studies on 713 cases of "viral" CNS disease in the same laboratory subsequent to 1953. With use of improved techniques a specific diagnosis was established in 521 cases (73%). More than 27 immunologically distinct viruses were implicated as well as leptospiras, tubercle bacilli, and fungi.

Specimens from hospitalized patients with acute CNS disease suggestive of viral infection were submitted between January, 1953, and January, 1958. These patients included military personnel, their dependents and veterans; the majority were children or young adults. In approximately 80% the illness was contracted in the United States and was sporadic in occurrence. Comparable numbers of patients were studied during each of the five years, with all seasons well represented. All specimens of serum and other material received were tested insofar as quantities permitted for evidence of infection with mumps, LCM, herpes simplex, Coxsackie, ECHO, poliomyelitis, and likely arthropod-borne viruses and leptospiras. Tests for evidence of infection by other viruses, Rickettsiae, tubercle bacilli, fungi, and Toxoplasma were done on certain specimens. Basic criteria for successful laboratory diagnosis of infection were demonstration of a significant antibody increase or recovery of an agent from autopsy specimens. These criteria were modified in certain instances.

A laboratory diagnosis was established in 71% of 430 cases with aseptic meningitis, 72% of 139 with encephalitis, and 81% of 144 with paralytic "poliomyelitis." The agents most commonly associated with aseptic meningitis were Coxsackie Group B (18%), mumps (16%), ECHO (12%), poliomyelitis (9%) and LCM (9%) viruses, and leptospiras (4%). Mumps and LCM viruses were also presumably causative in cases of encephalitis (16% and 14%, respectively). Other viruses apparently responsible for encephalitis included the arthropod-borne group (14%) and herpes simplex (9%). Paralytic disease without encephalitic features was virtually pathognomonic of infection with a poliovirus; in only three cases did a different virus appear to be responsible.

Enteroviruses accounted for 41% of all cases, including 156 with poliovirus, 82 Coxsackie, and 53 ECHO virus infections. All Group B Coxsackie serotypes except B-1 were encountered in relation to CNS disease, and strains of each of these four types were recovered from cerebrospinal fluid (CSF). Twelve ECHO virus serotypes

* By invitation.

were found in association with CNS disease and in seven instances one of three serotypes was isolated from CSF.

Viral infections of the CNS occurred in recognizable patterns of seasonal distribution. Such data used in conjunction with clinical, laboratory, and other epidemiological information provided the most effective criteria for clinical diagnosis.

Discussion

DR. HORACE L. HODES, New York: In the paralytic mumps case, do you remember where the paralysis was?

DR. HARRY M. MEYER JR.: I don't recall the exact location of the paralysis, but I think it involved the lower extremity.

DR. HORACE L. HODES: I was wondering because the few cases of mumps with paralysis that I've seen have always been of cranial nerves.

DR. ALEX J. STEIGMAN, Louisville: Dr. Meyer and his colleagues should be congratulated for applying recent techniques to bring light into this baffling field. I hope he will have the opportunity to continue to study the etiology not only of the encephalitic and aseptic meningitis patients but also of those with "paralytic poliomyelitis." Indeed, it is interesting that Dr. Meyer refers to this "diagnosis" on his lantern slides. Although it is apparent that the vast majority of instances of "paralytic poliomyelitis" are due to poliovirus infection, studies in my laboratory suggest the advisability of continued surveillance in order to be certain that viruses other than poliovirus are not acquiring increasing neurotropism, including paralytogenic properties.

Dr. Hodes referred to the likelihood of association of cranial nerve changes in mumps encephalitis. We have documented a triple simultaneous viral infection consisting of mumps, Poliovirus Type 1 and Coxsackie A14; bulbar paralysis and shoulder weakness were followed in a few days by parotitis. On purely clinical grounds such a child would have been regarded as having mumps meningoencephalitis with cranial nerve palsies, although a diagnosis of "paralytic poliomyelitis complicated by parotitis" would have been no less erroneous!

DR. HARRY M. MEYER JR.: Dr. Steigman, the virus laboratory at Walter Reed Hospital is still engaged in the study of "viral" central nervous system syndromes, and I imagine it will continue this line of investigation. Speaking in general about out studies of the "paralytic poliomyelitis" syndrome, we usually test first for evidence of poliovirus infection and only after that has been excluded investigate the possibility of infections with other agents. Paralytic cases that show no evidence of poliovirus infection, however, are studied for evidence of infection with most of the other viruses commonly associated with central nervous system disease.

In reference to the questions that you and Dr. Hodes asked about our case of mumps with paralysis, I now have the summary of that case before me. The patient was a 2-year-old girl who had an illness characterized by fever, meningeal irritation, and complete paralysis of the right leg. The child was left with a residual right foot drop. Sera obtained on the 7th and 30th days of disease demonstrated a significant increase in complement-fixing antibodies for mumps virus. Repeated attempts to isolate polioviruses from the stool of this patient or to demonstrate increases in neutralizing antibodies to polioviruses were negative.

4. **Infectious Hepatitis: Control of the Disease, and Detection of Virus During Incubation Period and in Subclinical Infection.** SAUL KRUGMAN, M.D.; ROBERT WARD, M.D.; JOAN P. GILES, M.D.*; OSCAR BODANSKY, M.D.,* and A. MILTON JACOBS, M.D.* Department of Pediatrics, New York University College of Medicine, New York.

Since 1953 approximately 500 cases of infectious hepatitis with jaundice have been observed at the Willowbrook State School. The studies to be described were concerned with attempts (1) to control the spread of the disease, (2) to determine the period of infectivity, and (3) to demonstrate viremia in a case of inapparent infectious hepatitis.

Prevention.—On Jan. 24, 1957, γ-globulin, 0.06 ml. per pound of body weight was administered to 1,182 patients. A comparable group of 1,771 persons served as uninoculated controls. At the end of the first year the number of patients no longer in the institution was subtracted from the above totals, leaving 1,120 persons in the γ-globulin group and 1,680 in the control group.

The results of observations for the two-year period following a single inoculation of γ-globulin are shown in Table 1.

* By invitation.

TABLE 1.—*Results of γ-Globulin Inoculation Over Two-Year Period*

Year	Group		Hepatitis with Jaundice: No. of Cases	Hepatitis with Jaundice: Rate/1,000/Annum
1957-1958 1st 12 mo.	Control	1771	39	22.5
	γ-G.	1162	3	2.5
1958-1959 2nd 12 mo.	Control	1680	15	8.9
	γ-G.	1120	8	7.1
1957-1959 Total-24 mo.	Control		54	15.7
	γ-G.		11	4.8

The findings for the first 12 months confirmed similar observations by Stokes et al., who reported prolonged protection following administration of γ-globulin to patients in an institutional epidemic of infectious hepatitis. During the second year of observation, however, there was no significant difference between the incidence of jaundice in the two groups. In an attempt to test the hypothesis of "passive-active immunity" the following study was initiated on Feb. 1, 1958: alternate patients, newly admitted to Willowbrook, were inoculated with γ-globulin, 0.06 ml. per pound of body weight. The results of observations for the past 15 months are shown in Table 2.

This study is still in progress.

Period of Infectivity.—A series of studies have indicated that virus is present in the stools and blood during the incubation period and early in the course of the disease. Stools collected at the following intervals have been shown to be infective: (*a*) 25th day of incubation period—two to three weeks before onset of jaundice, and (*b*) 1st to 8th day after onset of jaundice. Viremia was detected on: (*a*) 3d day of jaundice; (*b*) 3 to 7 days before onset of jaundice, and (*c*) 25th day of incubation period—2 to 3 weeks before onset of jaundice.

TABLE 2.—*"Passive-Active Immunity Test: Results of Fifteen Months' Observations*

Period	Group		No. of Cases of Hepatitis with Jaundice
Feb. 1, 1958, to May 1, 1959	Control	393	29
	γ-G.	367	10

This study is still in progress.

Inapparent Infection with Viremia.—A 6-year-old boy was fed the Willowbrook strain of infectious hepatitis virus. During the subsequent 66-day period of observation he had a normal temperature, good appetite, no vomiting, no hepatomegaly, no jaundice, and no biliuria. The serum bilirubin, thymol turbidity, and cephalin flocculation determinations performed on serial samples of serum obtained from 3 days before to 62 days after feeding of virus were normal. The serum glutamic oxaloacetic transaminase (SGOT), however, was normal until the 27th day (<50 units), rose significantly on the 34th day (155 units), reached a peak level of activity on the 37th day (250 units), and eventually returned to normal on the 48th day. It was postulated that this patient had inapparent infectious hepatitis with a 37-day incubation period as determined by the peak abnormal transaminase activity of the serum. Inoculation of the *37th-day* serum into eight presumably susceptible subjects was followed by hepatitis with jaundice in three patients—40, 47, and 48 days later. Hepatitis without jaundice was detected in three additional patients after 33, 37, and 47 days. These findings confirmed the presence of viremia in a patient with subclinical infectious hepatitis, the *only* abnormal finding being an increase in serum transaminase activity.

Discussion

DR. AUGUSTA B. MCCOORD, Rochester, N. Y.: What is the justification for feeding these children infectious hepatitis virus and causing them to be infected with the disease? Some years ago Dr. Arthur Kornburg showed that a group of medical students who had had infectious hepatitis in childhood still had various latent symptoms of the disease. Some people who have had infectious hepatitis apparently never completely recover.

DR. SAUL KRUGMAN: The decision to feed infectious hepatitis virus to mentally defective children at Willowbrook was not undertaken lightly. It was prompted by the unusual circumstances

which prevailed in the institution. Approximately 500 cases of hepatitis with jaundice had occurred over a five-year period. The disease in adults as well as children was particularly mild, and there were no deaths. The attack rate in newly admitted patients was enormous, and it was inevitable that most children would acquire the infection within the first six months after admission to this institution. Since infectious hepatitis is generally mild and benign in children, it was deemed feasible to induce the infection with the Willowbrook strain of virus in small groups under the most favorable circumstances, such as special isolation quarters and special medical and nursing personnel to provide close observation and care. The study group included only patients whose parents gave consent. A serious, uncontrolled endemic situation existed in this institution, and knowledge obtained from a series of suitable studies could well lead to its control.

We have conducted these studies for the past three years. In all instances the artifically induced disease, when apparent, was extremely mild and was followed by an uneventful recovery. In the majority of cases the infection was inapparent and could only be detected by biochemical tests of liver function. A retrospective review of the past three years of experience reveals that there has been ample justification for these studies.

DR. FREDERICK C. ROBBINS, Cleveland: First, it seems to me that your calculation of five months of protection is remarkably long and I would think considerably exceeds the life of γ-globulin in the patients' blood. Since the incubation period of the disease is 40 to 50 days, perhaps you should draw your line a month or a month and a half earlier.

Secondly, if you assume that the attack rate of the cases that continually occur in the control group represents the natural occurrence, this means that not all children are exposed at once and that there still are susceptibles in the remaining population. The rate of immunization due to the natural infection would be the same in the two groups, the inoculated and the controlled. The only difference would be that, provided active-passive immunity does occur, the cases in your inoculated group would not be apparent to you using the criteria that you have, namely, hepatitis with jaundice.

Therefore, after the γ-globulin effect has worn off, you would expect your rates to be exactly the same, which is just what you found. Unless you can think of a better explanation, I think you've essentially proved your point.

DR. KRUGMAN: In the study in which γ-globulin was administered to alternate patients on admission to the institution, 10 cases of hepatitis with jaundice have been observed in the γ-globulin group as compared with 28 cases in the uninoculated control group. Of the 10 cases of hepatitis which occurred in the γ-globulin group, 1 case was observed within the first five months after admission and 9 cases were detected after five months. Of the 28 cases of hepatitis which occurred in the control group, 19 cases were detected within the first five months after admission and nine cases were detected after five months. If the mechanism of protection were due to passive immunity only, it would be reasonable to assume that the attack rate in the γ-globulin group would be lower in the first few months but higher in the later period. Since the rates after five months were equal in both groups, it suggests that passive-active immunity may have been the responsible mechanism. This study is still in progress. More data will be required for an adequate analysis.

DR. JOSEPH STOKES JR., Philadelphia: I should like to mention a striking example of the circumstances under which the passive-active immunization, as described by Drs. Krugman and Ward, occurs. Dr. Drake of our Department, during an institutional outbreak, conducted a study with γ-globulin doses of 0.005 ml. per pound and 0.01 ml. per pound, which are minimal protective amounts. Liver function tests on all children (injected and controls) indicated infection without symptoms in large numbers of the children. There were relatively many more having hepatitis without symptoms in the γ-globulin group than in the controls, the latter group having a high rate of jaundice. Six boys with Entamoeba histolytica in their stools were separated from the cottages at the onset of the epidemic, were given γ-globulin, and again returned to the cottages after about 15 weeks, when it was thought the hepatitis outbreak had subsided. Despite the fact that no more children became jaundiced among those who had continuously lived in the cottages, three of the six boys who were returned had hepatitis with jaundice in about 21 days.

These findings well demonstrated (1) that when the passively immunized person continues to be exposed passive-active immunization occurs; (2) that when continuing exposure is absent the protection of the γ-globulin is limited in length.

Dr. Krugman's and Dr. Ward's work agrees with our studies that passive-active immunization occurs after doses of γ-globulin as high as 0.06 ml. per pound.

I should like to ask Dr. Krugman whether he found any evidence of chronic intestinal carriers of the virus.

The incubation period they have mentioned of about 30 to 45 days is certainly exceptional for the epidemic disease and suggests a difference in viral strains.

DR. KRUGMAN: We have not had an opportunity to test for a "chronic carrier state."

DR. C. HENRY KEMPE, Denver: Do you have any control data on the massive use of γ-globulin in the therapy of severe viral hepatitis?

DR. KRUGMAN: The patients who acquired hepatitis under our observation had either a very mild or inapparent infection. Without the aid of tests of liver function it would have been impossible to detect any signs of the disease. Consequently, γ-globulin was not used in this phase of our study.

5. Immunological Studies of a Nonpolysaccharide Fraction of the Hemolytic Staphylococcus Aureus. LT. ARTHUR NUNNERY (MC) U. S. N.*; MARY TINKER, M.S.,* and WILLIAM L. BRADFORD, M.D. Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester N. Y.

During preparation, a lipopolysaccharide fraction of hemolytic Staphylococcus aureus was found to contain a certain amount of protein. This led to evaluation of the nonpolysaccharide components of the organism. The preparation and immunological responses of such a fraction constitute the subject of this report.

Method.—A coagulase-positive strain of hemolytic Staphylococcus aureus (phage type: 52/42B/80/81) was grown in semisynthetic liquid medium for 24 hours and killed with 0.25% phenol. The mass of wet organisms collected in an angle centrifuge suspended in 0.85% sodium chloride (1 gm. per 4 ml. of salt solution). All procedures were carried out at 6 C.

After 24 hours the mixture was centrifuged. To the supernate, previously cleared by three centrifugations and filtering, was added 4 volumes of absolute alcohol. After 12 hours the white, flocculent precipitate was collected by centrifugation for one hour.

The precipitate was further purified by resuspension in a minimal amount of 0.85% salt solution and by reprecipitation with 4 volumes of alcohol. This procedure was repeated until the supernate no longer gave a positive Molisch test, was negative for reducing sugars, and failed to show an absorption of ultraviolet light at 265 MW.

The final yield was 10.4 mg. per gram of wet-weight organisms. It was free of reducing sugars, contained 2.2% nitrogen and 0.62% phosphorus, and was soluble in normal saline and in water. Calculated from its nitrogen content, the material contained approximately 15% protein.

The fraction was suspended in 0.85% sodium chloride containing merthiolate in 1:10,000 concentration. The strength used for skin testing contained 1 mg. of the fraction per each milliliter of diluent. The fraction was used to immunize rabbits, to coat erythrocytes for the hemagglutinin test, and to absorb agglutinins.

Direct macroscopic agglutination tests were carried out at a concentration of 1.27% to 1.5% sodium chloride in the serum antigen mixture, for preliminary observations confirmed the marked instability of the agglutination antigen of the Staphylococcus at the customary concentration of 0.85% sodium chloride.

Its protective quality was tested in mice against fatal challenging doses of the parent strain of organisms.

Results.—When 1/40 mg. of the fraction was injected intradermally into young infants, negative reactions occurred. Infants beyond 6 months of age, children, and adults usually gave either an immediate or a delayed type of response. Adults with the delayed type of skin reaction later showed three- to fourfold increase in their serum agglutinin titers; those with either negative or immediate type reactions failed to show increases of agglutinin titers.

Rabbits immunized intravenously or intradermally with the fraction developed significant agglutinin titers after eight weeks.

The material was active as a hemagglutinating antigen. In a series of mother-cord blood tests the mothers' serums consistently showed antibody, but in no instance was it demonstrated in the cord blood. Persons

* By invitation.

with a delayed type of skin reaction to the fraction usually showed no elevation of the hemagglutin titer. Like the clinical reaction, the hemagglutin titer appeared to be influenced by age. Intraperitoneal injection of the material subsequently protected 4-week-old white mice from fatal experimental infection.

Summary.—A nonpolysaccharide fraction of hemolytic Staphylococcus aureus was prepared by saline and alcohol extraction. This fraction, containing approximately 15% protein, was antigenic when injected into rabbits and man, and gave intradermal reactions in human subjects which varied with the age of the individual and during immunization with the fraction. The fraction demonstrated definite protective powers against experimental murine infection.

These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and the University of Rochester. NR 105-218.

Discussion

DR. ALFRED FLORMAN, Manhasset, L. I., N. Y.: The finding of an immunologically active nonpolysaccharide fraction of Staphylococcus is of great interest.

We too have been studying various fractions of the Staphylococcus in a search for an indicator of immunity to Staphylococcal infection. Most of our work was done with an antigen prepared by the method of Zepp from the supernate of an 18-hour culture in tryptase soy broth. This supernate was acidified, boiled over an open flame to reduce the volume, and then added drop-wise to 8-10 volumes of 95% alcohol. The precipitate which formed was our antigen. It was dried in vacuum and reconstituted with distilled water before use. It proved to be an excellent agent for sensitizing red blood cells for use in a hemagglutination test. Our work with this test will be reported later this week before the Society for Pediatric Research. The pertinent point at present is that we had our antigen analyzed chemically by Dr. Opper at the Mount Sinai Hospital. On the basis of what has been reported in the literature, we fully expected that this would be a lipopolysaccharide. We were therefore surprised when she reported back that carbohydrates were significantly missing, that the lipids were primarily neutral fats, and that the greatest portion of organic matter was protein. This is very suggestive of what Dr. Nunnery and his group have just reported.

DR. ARTHUR NUNNERY: We've had a great deal of trouble with polysaccharides and their general lack of specificity. They cross react as hemagglutinating antigens with streptococcal, pneumococcal, and meningococcal antiserum, and that is principally what led us to investigate these particular nonpolysaccharide fractions.

The trouble with the nonpolysaccharide fractions is that when they are diluted at 1 mg/cc. for skin testing or for immunization, positive tests for protein disappear. At this dilution the material is Millon and biuret negative, sulfosalicylic acid and phosphotungstic acid negative, and is negative to heat precipitation. Our biochemists cannot distinguish it from saline. How much this material was responsible for the immunologic results we obtained with our polysaccharide-containing fraction is, of course, unknown.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: Two things about Dr. Nunnery's work impress me. One is the simplicity of the method by which he gets his interesting material. I think very few of us look for anything good in ordinary "bath water"! As Dr. Nunnery said, after considerable effort, he decided to test this material which comes from the surface of the Staphylococcus by simply giving it a bath in normal saline. If one gives it a bath in twice normal saline, this interesting material does not easily come off, which, in itself, is quite interesting.

The second thing that interests me is the fact that the fraction protects mice against a fatal experimental infection. I believe that when such material protects, it's worth further study.

DR. RALPH WEDGEWOOD, Cleveland: Would you make some comments on the strain specificity of the fraction?

DR. NUNNERY: We cannot comment on that at this time, for our results to date are not significant at the 5% level. The trends are very interesting, and the agglutinins are specific for staphylococci. Our work in typing strains of staphylococci is at present incomplete.

6. Galactosemia: A Biochemical Study with Special Reference to the Genetic Mechanism and Mental Retardation.

KENNETH HUGH-JONES, M.D., M.R. IRENE HUANG, PH.D.,* and DAVID YI-YUNG HSIA, M.D.* Northwestern University, Chicago. Introduced by John A. Bigler.

Galactosemia is a hereditary disorder of carbohydrate metabolism characterized by

* By invitation.

vomiting, diarrhea, jaundice, hepatomegaly, and failure to thrive in early infancy. Recently, Isselbacher and his co-workers have shown in deficiency of the enzyme galactose-*l*-phosphate uridyl transferase (P-Gal-uridyl transferase) in the red blood cells of patients with this disease.

Some studies on the genetic mechanism of galactosemia will be described. In the first place a genetic analysis of 93 families reported in the literature suggested that the disease is transmitted by a single autosomal recessive gene. Next, the mean P-Gal-uridyl transferase levels in the blood was found to be 2.9 ± 1.1 units/gm. Hgb among 23 heterozygotes as compared with 4.6 ± 1.2 units/gm. Hgb in 16 normal controls ($t = 4.4$ d. f. $= 37$. $p = 0.0025$). Recently, we have had the opportunity of confirming the genetic mechanism in a large family with galactosemia. Enzyme assays revealed an affected adult, showed that all his six offspring were heterozygotes, and finally that one of these had married another unrelated heterozygote and they had produced four children, two of whom were affected.

The normal intelligence of these three affected persons, together with others reported in the literature and in our own experience, prompted an investigation into some of the factors relating to mental retardation. Analysis of our laboratory data from 14 persons over the age of 4 years, with galactosemia, suggested that there might be a correlation between the enzyme level and later intelligence ($p = 0.027$). Also, it was found that there was a definite inverse correlation between the maximum blood galactose level reached during a standard galactose tolerance test and the enzyme level in the blood ($r = .73$ $p = < 0.01$). An inverse correlation was also found between maximum blood galactose levels and intelligence using data reported in the literature ($p = < 0.01$), thus confirming the first observation. Finally, analysis of the literature showed that there was some correlation between an adequately controlled diet from an early age and later intelligence.

From this data it was felt that diet and the inherent enzyme level may both be factors in deciding the outcome of a galactosemic patient's intelligence.

Discussion

Dr. Milton Rappaport, Philadelphia: I should like to ask whether information or data has been gathered on aminoaciduria in these patients. What I gather from reading is that this is a rather sensitive indicator of the presence or absence of galactose in the diet. Was the presence of aminoaciduria used to separate patients into those that were on galactose-free diets from those in whom dietary control was inadequate?

Dr. George Donnell, Los Angeles: We too have been very much interested in the general problem of mental retardation and galactosemia. The availability in our clinic of 15 galactosemic families has permitted longitudinal studies of a large number of affected children.

In the course of our investigations careful studies on the use of the galactose tolerance test as a possible means of identifying the heterozygote were carried out. All members of the families were tested along with a series of normal controls. Our results have shown no correlation between an arbitrary response index and intelligence quotient in the galactosemic child. This was also true of the maximum galactose level reached during the galactose tolerance test.

One of the factors that has been very apparent to us is that the galactose tolerance curve is not a reproducible measurement in the same individual from time to time. Although abnormal in each instance, the height and shape of the curve will be variable.

More recently, employing a modification of the original assay for phospho-galacto-uridyl transferase, similar results were obtained. In the case of the homozygote the values for the most part were zero with only 2 out of 13 values showing a trace of activity.

This is consistent with the findings of Kalckar and his associates and those of Kirkman. In the heterozygote, the failure to find a correlation between either a galactose tolerance index or P-Gal transferase level in the erythrocyte is understandable. In the one case, the oral galactose tolerance includes factors other than the primary difficulty in the liver. In the other case, the presence of the enzyme system in the erythrocyte, although reflecting the genetic transmission, is in no way a measure of the total enzyme available in the

liver, and consequently is not a measure of the total physiological capability.

DR. GEORGE M. GUEST, Cincinnati: There is much evidence that galactosemic children gain in tolerance with increasing age. Could Dr. Hugh-Jones comment on the quantitative aspects of the development of the collateral pathways?

DR. AUDREY K. BROWN, Detroit: To enlarge a little on Dr. Guest's question, I would like to know whether the authors have any data concerning the development of the possible alternate pathway for galactose metabolism involving uridine diphosphogalactose pyrophosphorylase, which, according to Dr. Isselbacher, is deficient in the newborn and gradually develops. It would seem that variation in the time of development of such an enzyme system might lead to variation in any effect attributable to the major defect in galactosemia.

Further, from the data presented it is difficult to see how one can actually detect an *individual* heterozygote by the method presented. There seems to be overlap in values for the heterozygote and the normal.

DR. ROBERT E. COOKE, Baltimore: I'd like to ask the authors whether or not they were able to make any correlation between the enzyme levels or the height of the galactose tolerance rise in the mothers of infants who had adequate diets but who had mental deficiency. I think this is a critical group and one that we have the least information about.

DR. JULIUS B. RICHMOND, Syracuse, N. Y.: I think this is very interesting material. I would like to introduce one reservation. It is important to note that when one tests intelligence, one is testing many functional capacities. I think a numerical recording of the "I. Q." as has been presented here may not be a real reflection of the various intellectual potentialities which a given child may have. I think it introduces a very complex variable in this whole situation and may account for some of the difficulties in explaining the results. The complexity of this variable may also explain why some of the discussants have not obtained similar results.

DR. KENNETH HUGH-JONES: If I could deal with the last point first because it is freshest in my mind.

We realize that many variables enter into the make-up of one's actual I. Q. value, as Dr. Richmond has pointed out. In fact, when we tested intelligence quotients against enzyme levels the correlation was not significant. But I do not think that the enzyme levels play any part in variations within the normal range, i. e., I. Q.'s from 90 to 140. On the other hand, I think the enzyme value may be significant when the value is very low. Children in this group may well be retarded. For this reason, we merely divided our cases into those of normal intelligence, above 90, and those who were retarded. I think this, too, may be why Dr. Donnell found no correlation between intelligence quotients and enzyme values.

In reply to Dr. Rappaport, the cases used for the dietary analysis were drawn from the literature; many before testing the urine for amino acids became a routine in galactosemia, so we were not able to use this as a yardstick of the adequacy of dietary control. In the earlier literature, proteinuria was often noted, and this cleared rapidly if the diet was galactose free. When there was information about either aminoaciduria or proteinuria, its disappearance was used as a check on the diet.

I am afraid, Dr. Guest and Dr. Brown, we have done no special studies on the alternative pathway of galactose metabolism described by Isselbacher. From our own data we have no evidence of improved galactose tolerance with age; this may be because we tended not to do galactose tolerance tests in the neonatal period. We have done enzyme assays throughout galactose tolerance tests but have not shown any significant variation in the values obtained.

Dr. Brown, I did mention in concluding that we do not suggest that this method will detect an individual heterozygote or that it is necessarily the best method available; but, just that with this relatively simple method we were able to show that a group of known heterozygotes had a very significantly lower enzyme level than normal controls.

In reply to Dr. Cooke's important question, there was a correlation between those who were retarded in spite of adequate dietary, and their maximum blood galactose levels. In the six cases in this category, four had had galactose tolerance tests done. Their mean peak value was 360 mg/100 ml.; this is higher than the mean for the total retarded group, suggesting that they had even less enzyme, but the numbers are too small to make this necessarily significant. In our own three retarded cases, one had had an inadequate diet because he was not diagnosed until he was nearly 3 years old. One treated from the age of 3 months had the highest galactose level of all our cases, and we could detect no enzyme. The third, who was only slightly retarded (I. Q. 81), had a moderately elevated galactose level, an enzyme value of 0.3 units/gm. Hgb., and adequate dietary control from the age of 2 months. These are too few cases to be certain, but is it possible that if the patient is in the upper half of the range for galactosemics he has sufficient enzyme to protect himself from the cause of nerve damage. At a lower enzyme level he escapes brain damage provided galactose is kept low in his diet and those that have no enzyme may find the minimal

amounts of galactose in most so-called "galactose-free diets" too much.

7. Observations on the Significance of Primaquine-Sensitive Erythrocytes in Patients with Congenital Nonspherocytic Hemolytic Anemia. WILLIAM H. ZINKHAM, M.D.,* and RAYMOND E. LENHARD JR.* The Johns Hopkins Hospital, Baltimore. Introduced by Robert E. Cooke.

The term "congenital nonspherocytic hemolytic anemia" has been applied to a variety of congenital hemolytic disorders, and a review of reported cases indicates that not all patients with this diagnosis are suffering from the same disease. The mechanism of the metabolic defect in erythrocytes from these patients has recently been investigated. Dacie demonstrated in one type that the rate of autohemolysis in vitro was not only enhanced but also unaffected by the addition of glucose. Newton has reported a deficiency of glucose-6-phosphate dehydrogenase (G-6-P. D.) in several families of Italians with a nonspherocytic hemolytic syndrome. This biochemical abnormality is similar to that observed in normal persons of certain ethnic groups—Negro, Eskimo, Sephardic Jew, Italian, and Greek—who are susceptible to the hemolytic effects of primaquine. Since Newton's cases involved members of a racial group in which the incidence of the G-6-P. D. deficiency is approximately 10%, the question of chance association has been raised. Furthermore one wonders if all patients diagnosed as "congenital nonspherocytic hemolytic anemia" will manifest a similar enzymatic abnormality.

Over the past two years studies of glutathione metabolism and G-6-P. D. activity have been done on red cells from six patients with a nonspherocytic hemolytic anemia. These patients are members of four families, one being American Negro (R. J.), and the others, American Caucasians of Dutch, French, and English ancestry. All of these patients developed hyperbilirubinemia in the neonatal period, but their clinical courses thereafter have differed. Two of the patients, R. C. and R. J., required frequent transfusions before splenectomy at 2 and 3 years of age. Even though hemolysis continued after splenectomy, transfusional requirements greatly decreased. Target cells and punctate basophilia of the red cells were present in the peripheral blood. In the remaining four patients the degree of anemia was milder; the rate of hemolysis was occasionally accelerated after infections, and morphology of the erythrocytes was normal. One of these patients experienced a severe hemolytic episode following ingestion of phenacetin.

Glutathione values before and after incubation of whole blood with acetylphenylhydrazine (glutathione stability test) and assays for red cell G-6-P. D. activity were normal in patients R. J. and R. C. Erythrocytes from the other four patients manifested a markedly abnormal glutathione stability test and an extreme reduction of G-6-P. D. Similar studies on the families of these four patients indicate that these defects are transmitted by a sex-linked gene, and that clinical hemolysis occurs only in persons with a marked deficiency of G-6-P. D. In one of the families this correlation was demonstrated in three generations. The female carrier had only a partial reduction of G-6-P. D. activity, and her peripheral blood findings were normal.

On the basis of these findings one should be able to specifically categorize a certain per cent of patients now included in the polyglot known as "congenital nonspherocytic hemolytic anemia." In this type of the disease the morphology of the red cells is normal; the degree of anemia is mild except during certain infections; G-6-P. D. activity of the erythrocytes is reduced, and the defect is transmitted by a sex-linked gene. Individuals with this type will also be susceptible to the hemolytic effects of those drugs and chemicals which can he-

* By invitation.

molyze erythrocytes of primaquine-sensitive persons.

Discussion

DR. WILLIAM NEWTON, Columbus, Ohio: It is gratifying to have Dr. Zinkham confirm our findings reported last spring, that congenital nonspherocytic anemia patients may show a primaquine-sensitive defect in their red cells.

The data presented today by Dr. Zinkham would suggest that this syndrome is a variation of the larger clinical problem of a group of Negroes and limited number of Caucasians who have the same red cell enzyme defect, yet do not show increased hemolysis unless exposed to primaquine or related drugs.

While this may be true, I think that it should be pointed out that all of the children described by Dr. Bass and me, as well as most of those described by Dr. Zinkham today, are Caucasian. If this congenital red cell defect is simply a variation of the typical nonanemic, primaquine-sensitive subject, then one would expect a preponderance of Negroes in a group similar to that which he is describing today.

The second point of difference between these two groups of patients that should be mentioned, is that the enzyme defect in the mothers of these children described today by Dr. Zinkham appears to be milder than that seen in the nonanemic, primaquine-sensitive individual female carrier. As you know, it is now felt that this defect is transmitted through females who show an intermediate enzyme defect, to males who show the severer hemolytic process when exposed to these drugs.

Since these children with chronic nonspherocytic hemolytic anemia have a much severer process, resulting in continued hemolytic anemia in the absence of drug exposure, and also in the laboratory as demonstrated by an almost complete absence of the enzyme, one would expect their mothers to show severer changes in their red cell enzyme levels. This does not appear to be true, as Dr. Zinkham has pointed out.

There is an additional paradox. Despite the fact that these mothers' enzyme levels are not strikingly altered, they still show, in some instances at least, a functional red cell defect in that their red cell survival may be definitely reduced. For instance, one of the mothers had a mean red cell survival of approximately 60 days.

My first question to Dr. Zinkham refers to the enzyme level in the red cells in the mother of his family "R." Did I understand that her enzyme level was 185 units? This would appear to be within the range of normal value. Secondly, I would like to ask him whether or not he has done any red cell survival determinations on the mothers of the children either of the typical nonanemic primaquine-sensitive patients, or the mothers of these children he has described today. And thirdly, I would like to ask whether or not he has observed inclusion bodies in the red cells of these patients after splenectomy. We have observed definite inclusion bodies in the red cells of the patients who have been thus treated.

Since describing our families we have studied one patient who we think represents a variation of this picture. He happens to be an adult who came in to have us investigate an anemia of his son. The son turned out to be normal, but the father was polycythemic with a hemoglobin concentration of 17 gm., significant reticulocytosis, and a compensated hemolytic anemia. His red cells showed an almost complete absence of this enzyme.

In our patients with this disorder who have been splenectomized, all have had inclusion bodies in the red cells after splenectomy. Have you observed this among your patients?

DR. WILLIAM H. ZINKHAM: It is no more difficult to determine the carrier state of the mother whose sons have nonspherocytic hemolytic anemia, than of mothers whose sons are primaquine-sensitive. In one of our mothers, for example, the results of the glutathione stability test and the assay for glucose-6-phosphate dehydrogenase activity were definitely in the intermediate range. The other mother, to whom Dr. Newton refers, had an enzyme level which was in the low normal range, and her glutathione stability test was borderline. The activity of glucose-6-phosphate dehydrogenase in this mother's erythrocytes was subsequently measured by another method, the "derived" assay technique of Glock and McLean. This procedure is probably a more accurate assay of glucose-6-phosphate dehydrogenase activity, and, when it was applied to the red cells of this mother, values in the intermediate range were obtained. A similar experience has been encountered in some heterozygote women whose sons have primaquine-sensitive erythrocytes. Here, too, the "derived" glucose-6-phosphate dehydrogenase method is a better discriminant of the female carrier.

We have not determined the life span of the red cells in our mothers whose sons have congenital nonspherocytic hemolytic anemia. Red cell survival times in primaquine-sensitive female heterozygotes who are not exposed to drugs are normal.

DR. AUDREY K. BROWN, Detroit: In the third group of patients that you described, what was the rate of glucose utilization? As I understand that slide, there was a marked fall in the reduced glutathione levels in the absence of glucose. Did you find an increased glucose utilization rate?

In the first group of patients described, did you study the compensatory pathways? Was there a difference, for example, in aldolase activity or glutathione reductase activity?

DR. ZINKHAM: Glucose utilization studies have been done on the red cells from the patient in Group III, but the results are not yet available.

The only other enzyme assay done on the red cells from patients in Group I was for 6-phosphogluconic dehydrogenase activity. Levels for this enzyme were normal or slightly increased.

DR. RUTH GROSS, San Francisco: I think that it's important that we continue our efforts to elucidate the enzyme defect in congenital nonspherocytic hemolytic anemia and I want to congratulate Dr. Zinkham for his efforts in this regard.

I want to ask him, however, if he doesn't think it more likely that there may be an association here of two genetic defects rather than an influence of the glucose-6-phosphate dehydrogenase deficiency on this disorder.

We have noticed that in families who have fava bean hemolytic anemia (these are Caucasian families of Italian or Greek descent) that there tends to be an extremely low level of glucose-6-phosphate dehydrogenase. For instance, we were fortunate enough to study one family in which we could measure the enzyme level in 36 individuals in three generations. Every affected individual in this family, that is, every homozygote in this family had a zero level of glucose-6-phosphate dehydrogenase. There was no evidence whatsoever, Dr. Zinkham, of increased hemolysis in this particular family, and I doubt from our experience and those of the Israelis and Italians who have also found such low levels of this enzyme in certain individuals with favism that the inability to detect enzyme activity can readily be related to the abnormalities that you observed in these studies. It seems to me that there is some other interpretation, and I personally am more interested in the connection between the two genetic defects than the influence of absent glucose-6-phosphate dehydrogenase activity upon chronic hemolysis. I wonder if you'd comment on that.

DR. ZINKHAM: Dr. Gross has posed a very important question regarding the etiologic role of the enzyme deficiency in our patients with congenital nonspherocytic hemolytic anemia. It is true that multiple genetic factors, or possibly even a combination of genetic and nongenetic factors, may be involved in the pathogenesis of this disease. On the other hand, I feel that the complete absence of glucose-6-phosphate dehydrogenase activity in the red cells of these patients is of special importance and that the observations cited by Dr. Gross do not detract from its significance. Primaquine-sensitive Greeks, Italians, and Sephardic Jews frequently have no detectable enzyme activity in their erythrocytes. During an episode of drug- or fava bean-induced hemolysis, however, enzyme activity increases with elevation of the reticulocyte count. In the patients with congenital nonspherocytic hemolytic anemia, there is no detectable enzyme activity in spite of reticulocyte counts being always in the range of 10% to 15%. On the basis of this comparison the enzyme abnormality appears to be severer in these patients, and therefore may be the most important factor in hastening the in vivo aging of the erythrocytes.

8. Salt Restriction and Salt Load in Cystic Fibrosis of the Pancreas. PAUL A. DI SANT'AGNESE, M.D., and ALFREDO M. VIDAURRETA, M.D.* Department of Pediatrics, College of Physicians and Surgeons, Columbia University, and the Babies Hospital, New York.

During "salt restriction" all of the subjects were placed for a period of five days (1) on a diet low in sodium chloride content; (2) on either desoxycorticosterone acetate (DCA) or fludrocortisone (9 α-fluorohydrocortisone). Sweat tests were obtained before and after this period of time.

In five normal controls the sweat electrolyte concentration dropped after the study period an average of 54% below the original values; a normal response expected from the previous studies of Conn and others.

In contrast, in nine patients with fully manifested cystic fibrosis sweat electrolyte levels dropped to only 9% below the much higher original values after the five-day study. This confirms our original observation that patients with this disorder are unable to conserve salt through their sweat glands in response to various stimuli.

In four parents of index cases there was a drop in sweat electrolyte concentration of more than 50% from the original high levels and average normal values were reached after the test period.

Three adults with generalized obstructive emphysema had a drop of 56% in the abnormally high original values for sweat electrolytes and reached normal levels after the five-day period.

* By invitation.

In addition eight patients were tested who had cystic fibrosis, chronic lung disease, and high sweat electrolytes, but normal pancreatic trypsin. In five instances the sweat electrolyte concentrations did not decrease significantly after the test period, while in three others they dropped 50% below the original levels and to high normal values.

It was concluded that there was a difference in behavior of sweat electrolytes between patients homozygous for cystic fibrosis and individuals heterozygotic for this disorder. Whereas the former cannot conserve salt via their sweat glands during hot weather, salt restriction or the administration of DCA, the latter are able instead to conserve salt normally in the sweat following a variety of stimuli. The importance of these findings in properly evaluating genetic studies is pointed out. The possibility is also raised that the enzymatic or other basic defect in cystic fibrosis may be present in different degrees and thus lead to varying clinical manifestations.

Experiments on the effect of oral salt loading on sweat electrolytes have been performed so far on three control subjects, four patients with completely manifested cystic fibrosis, and five parents of index cases. The results of these studies will be presented.

Discussion

Dr. William M. Wallace, Cleveland: I am sure that you are aware of the observation that the concentration of electrolytes in sweat is related to the rate of sweat production. When cystic fibrosis is present, measurement of sweat electrolyte concentration alone certainly gives a clear-cut answer to the question we wish to know. However, if one wishes to identify the heterozygote, I wonder if utilization of the concentration: rate index as originally described by Locke and associates (Locke, W.; Talbot, N. B.; Jones, H. S., and Worchester, J.: *J. Clin. Invest.* 30:325, 1951) might not be helpful?

Dr. A. di Sant'Agnese: Dr. Wallace, we have not taken the rate into account at the present time. However, some years ago we compiled the sweating index as described by Talbot in some patients with cystic fibrosis. As it seemed to check pretty well with the other figures, we have not used the index subsequently.

Dr. Arden Miller, Kansas City, Kan.: According to your slides, the youngest children whom you tested were about 2 years of age. Do you have any data or notions about whether younger children respond differently?

Dr. di Sant'Agnese: We have not given steroids to infants, but we have put four or five of them for different reasons on oral salt restriction and they respond similarly to the older children.

Dr. Murray Davidson, New York: I would like to thank Dr. di Sant'Agnese for showing these results to help us explain those found in a patient with whom he is familiar and in whom a similar result has remained unexplained for four years. This was a young 11-year-old Sephardic Jew with pulmonary disease, high sweat electrolytes, but normal duodenal tryptic activity. One hour after he was given an injection of pancreozymin, a pancreas-stimulating hormone, the secretion of sweat electrolytes would be reduced to normal levels. We have not been able to repeat these observations in any other patient, in spite of the fact that this was observed in this patient on three separate occasions. I should like to ask Dr. di Sant'Agnese two questions.

First of all, in our patient the viscosity of the duodenal fluid was elevated in spite of the fact that the tryptic activity was normal. Did you measure the viscosity in your patients with normal trypsin who displayed this same trend with restriction of salt intake?

Secondly, are you suggestiong that the patients with pulmonary disease and normal tryptic activity may be heterozygotes or that they are variants of the full-blown picture?

Dr. di Sant'Agnese: Dr. Davidson, I do not know how to interpret the experimental results you obtained with this one patient.

We do not test the viscosity of duodenal fluid by viscosimetric methods, grading viscosity roughly by inspection only. I therefore have no data with which to answer your question.

As to the third point, I think the number of patients is too small to make any suggestions, and I would like to limit myself to a presentation of the factual data only.

Dr. Robert S. Ely, Little Rock, Ark.: The Addison disease group is the only other where abnormally high sweat electrolytes are found. In these the electrolyte concentration is reduced after administration of desoxycorticosterone. Conversely Dr. di Sant'Agnese has just shown that the children with cystic fibrosis do not exhibit this type of response. In line with this, Dr. Charles Lowe has suggested that cystic fibrosis may reflect a Seabright-Bantam-like syndrome, with lack of normal end organ response. Certainly the pattern

of corticosteroid production and metabolism seems normal in these children, at least in those we have studied.

Dr. di Sant'Agnese, I'd like to ask if you have checked the sodium-potassium ratio in the sweat of these children, as it could be a sensitive index in those cases where the sodium change itself is not great and thus help identify the heterozygous type.

DR. DI SANT'AGNESE: Dr. Ely, in the last few years we have not determined the sweat potassium content. I therefore have no data with which to answer your question.

9. The Incidence of the Female Sex Chromatin Pattern in Mentally Defective Males. H. DAVID MOSIER, M.D., and LAWRENCE W. SCOTT. From the Department of Pediatrics, University of California School of Medicine, Los Angeles, and the Pacific State Hospital, Spadra, Calif.

The occurrence of the female sex chromatin pattern in an apparent male is usually accompanied in the postpubertal period with changes known as Klinefelter's syndrome. The incidence of this defect in the general population has been estimated to be 1 in 1,000. Recent reports have indicated that there is a higher frequency in mental defectives.

The frequency was investigated in 886 mentally defective male inpatients in a state hospital in California. Seven positive cases were found, giving an over-all incidence of 0.79%. The ages of the seven ranged from 7 to 38 years. The youngest was prepubertal, and the remaining were sexually mature. The testes were smaller than normal in the latter group, but normal for the age in the 7-year-old patient. There was minimal gynecomastia in five of the postpubertal patients. The 17-ketosteroids were within normal limits in five and slightly below normal in two. The gonadotropins were normal or slightly elevated in the postpubertal cases. The I. Q. ranged from 22 to 66 in the group of positive cases. A few stigmata of Mongolism were present in one of the cases, and the youngest of the cases had a Mongoloid half-sib. Testicular biopsies revealed typical changes of Klinefelter's syndrome in the postpubertal patients. In the prepubertal patient little alteration was seen. There was some germinal epithelium present but this appeared to be reduced in amount.

A preliminary analysis of the data suggests that the combined defect of Klinefelter's syndrome and the female chromatin pattern is more likely to be associated with mild mental deficiency. Studies are in progress to further characterize the psychologic abnormalities in this group of mental defectives.

Discussion

DR. ANDRE PRADER, Zurich, Switzerland: Dr. Mosier has mentioned our findings. We examined 332 mentally defective boys of mild mental deficiency and found 8 cases. This is one in 42. In addition we did a control group of highly intelligent boys and found in a group of the same number no cases. So I think it confirms all Dr. Mosier has found.

DR. MELVIN GRUMBACH, New York: Dr. Selna Kaplan and I, in collaboration with Dr. Stimpson, have for some time been surveying the nuclear chromatin pattern in mentally defective boys in a state institution. Our results also indicate that the incidence of males with chromatin-positive nuclei is lower in severely retarded subjects than that which has been reported in mentally retarded boys with higher I. Q.

Another point of interest is the fact that chromosome anomalies are not rare, and represent an important cause of developmental defects in man. Three chromosome abnormalities have already been identified: 1. In typical cases of the syndrome a gonadal dysgenesis with chromatin-negative nuclei an XO constitution has been described. 2. Chromatin-positive cases of seminiferous tubule dysgenesis (Klinefelter's syndrome) have been shown to have an XXY or an XXY/XX sex chromosome constitution. 3. A diploid number of 47 chromosomes has been found in cases of Mongolism; the extra chromosome appears to be a triplicate of one of the small acrocentric chromosomes. There is good evidence stemming from observations in 1916 by Bridges in Drosophila, and recently in the mouse, that such chromosome anomalies can arise from accidents at meiosis due to nondisjunction. These would lead to sperm or ovum which either lacks a chromosome or which contains an extra chromosome. Investigation of patients with gonadal dysgenesis or seminiferous tubule dysgenesis and their families for sex-linked recessive characters should provide an opportunity

to determine whether spermatogenesis or oogenesis might be defective.

It is of interest that the incidence of Mongolism which involves an abnormality of the autosomal chromosomes is 1 in 500 to 1 in 600 liveborn infants. A similar incidence has been found in chromatin-positive seminiferous tubule dysgenesis, a disorder in which there is an abnormal number of sex chromosomes. In a survey of 3,715 newborn infants Keith Moore found that 1 in 360, or 0.26%, apparent male infants had chromatin-positive nuclei and presumably were aneuploids.

These remarkable new developments in cytogenetics supply additional evidence that the sex chromatin mass in chromatin-positive persons probably represents heterochromatic portions of 2 X chromosomes. However in certain abnormalities of sex differentiation there may be an abnormal number of sex chromosomes, in which case the sex chromatin pattern provides information on whether or not the patient has 2 XX chromosomes. Despite this limitation the nuclear chromatin test has been of great value in diagnosis. Individuals who lack a sex chromosome or who have an XXY constitution are neither chromosomal males nor females. It is now well recognized that the sex chromosomes are not an absolute determinant of psychosexual orientation.

10. Relapse in Nephrosis Following Prolonged Remissions. HOWARD G. WORTHEN, M.D.*; IDA GANS, M.D.*; ROBERT L. VENIER, M.D.,* and ROBERT A. GOOD, PH.D., M.D. Department of Pediatrics, University of Minnesota, Minneapolis.

A common program for the management of patients with nephrosis is the use of adrenal steroid hormones to induce a remission, followed by prolonged interrupted steroid therapy in an attempt to maintain the remission. Exacerbations of nephrosis shortly after stopping this interrupted therapy are frequently observed, but exacerbations after longer intervals are considered to be uncommon.

While following a group of approximately 90 nephrotic children, we have observed 5 patients who had exacerbations of nephrosis at intervals of from 3 to 22 months after interrupted adrenal steroid therapy was discontinued. All five of these patients had the characteristic clinical findings of "pure" nephrosis, without hematuria, hypertension, or evidence of impaired renal function. The initial diuresis was produced with little difficulty, and they had all remained well, with no clinical or laboratory evidence of nephrosis, for at least one year while on the interrupted steroid program.

All of the patients were studied by clearance techniques before the initial therapy was begun. Only one patient had a reduced inulin clearance, and the clearance in this patient had returned to normal during the period of treatment.

Renal biopsy specimens, obtained from four of the patients while they were in remission, showed normal morphology in all. Electron microscopy of this tissue showed that the characteristic foot process lesion of the glomerular epithelial cell had reverted to normal.

The late recurrences pose several questions, both practical and theoretical. The chief clinical problem is the increased difficulty in prognosis which arises because of the possibility of a late exacerbation, even in a patient who has remained free of all signs of nephrosis while receiving interrupted adrenal steroid therapy.

None of the techniques we employed was of benefit in separating these 5 patients from the group of 30 patients who have remained well after the interrupted therapy was discontinued. This failure underscores the caution which must be exercised when attempting to predict the outcome of nephrosis.

Although the use of a planned program using adrenal steroid hormones following initial diuresis has apparently improved the prognosis in nephrosis, the mechanisms by which these agents act to produce the improvement is unknown. The occurrence of relapses during the interrupted therapy, or just after the therapy is terminated, suggests that the adrenal steroid hormones act by suppressing the disease which would otherwise be manifest. However, very late recurrences, observed in some of the cases,

* By invitation.

suggest that the disease may have been "cured" by the initial treatment, and that it has recurred in a susceptible patient following exposure to a new "nephrotogenic" stimulus.

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Discussion

Dr. Robert J. McKay, Burlington, Vt.: During the past September in a three-week period in a small group of nephrotic patients, we had what looked like three relapses.

Two were in patients who had been off steroids for between 6 and 12 months. These were both adults.

During the same three-week period we had a third patient who was on intermittent steroid therapy such as you described and who had a urinary relapse and ran 4+ proteinuria for about 10 or 12 days. He had not done this for about a year although he has been running a trace to a 1+ right along.

I'd like to ask Dr. Worthen if his group has made any attempt to analyze his patients as to time of year of the relapse and possible relationship to possible allergens (pollens) which might occur at a particular time of year.

Dr. Howard G. Worthen: Dr. McKay, your observation that relapses occur frequently during the pollen season is very interesting, particularly since so many nephrotic children have allergic backgrounds. We have not yet seen any consistent relationship such as you describe, but we shall be more alert for this possibility in the future.

Dr. Jerome L. Kohn, New York: A young child with generalized edema was admitted to the Mount Sinai Hospital in 1949. This was before the advent of the corticoids. After several months there was a spontaneous remission. Except for a mild albuminuria he was well for the next eight years. He was then admitted to the Babies Hospital with generalized edema. He responded promptly to a course of corticosteroids. At present he is leading a normal life. He still has a mild albuminuria. His urea clearance test is normal. Whether this is a recurrence of the original illness may be questioned? This child was also observed by Dr. Conrad Riley and Dr. Ralph Moloshok.

Dr. Kurt Lange, New York: Most of us who have seen a large group of patients with nephrosis have had experience similar to that of Dr. Worthen. Occasionally a patient who is in complete remission after the end of prolonged steroid therapy will relapse. Such instances, however, are rather rare in our material. Knowing that Dr. Worthen's group sees a considerable number of children with nephrosis, I would like to ask whether the five cases presented do not represent only a small percentage of the cases treated.

I also wonder whether one needs electron microscopy to make a statement about the complete remission of such cases. From the evidence submitted by many observers it appears that the smudging of the epithelial foot processes is only a reaction of the kidney to severe proteinuria; so the return of electronmicroscopic changes to normal indicates in my opinion not much more than the disappearance of an abnormal proteinuria. Dr. Worthen has speculated that a specific virus may possibly be the cause of the disease and of relapses. While some relapses occur without precipitating causes, the majority occur after upper respiratory infections, after measles, varicella, and pneumonias. It may be difficult to find a common viral denominator for these precipitating causes for the relapses.

In addition, however, there are other findings where patients with nephrosis have relapsed after active immunization, e. g., DPT, smallpox, etc. In addition, we have recently observed two relapses after polio vaccination and we were informed about one case where the primary attack occurred within 14 days after polio vaccination. This might have been completely coincidental. The patient was then treated with steroids and was free of signs and symptoms of the disease for five months. He then received a second polio injection followed by an immediate relapse of the nephrosis. While this again may be a coincidence, it is at least highly suggestive.

I, therefore, wonder whether we should not stick to the explanation that relapses may occur in any situation where antibody formation is stimulated and where with the specific anamnestic response a nonspecific anamnestic response is apt to occur.

Dr. Howard G. Worthen: In regard to the number of cases, we are following about 90 patients at the present time, of whom 30 have remained well for over a year after interrupted cortisone was stopped. The cases reported here, therefore, represent about 5% of the total cases and about 15% of those who are apparently well off therapy.

Dr. Lange, your comments regarding the cause of the relapse are very appropriate. Certainly the bulk of evidence favors the theory that a relapse might be caused by any of a large number of nonspecific stimuli which sets in motion an antigen-antibody reaction. However, I would like to stress the point that this theory is not proved, and that we should continue to search for a specific agent which might be amenable to specific therapy.

Dr. Allan Butler, Boston: I wonder if you have any good evidence that what you call "inter-

rupted" cortisone therapy has advantages over daily cortisone therapy. We started using "interrupted" therapy quite a number of years ago thinking perhaps it did have advantages. But we came to the conclusion it didn't, and we now are using daily instead of "interrupted" therapy. So we would like to have the benefit of your wisdom as to evidence showing that "interrupted" is better than daily therapy.

DR. WORTHEN: I am hardly qualified to answer that, Dr. Butler. The treatment of nephrosis is so empirical that the choice of a particular routine seems to depend more on personal opinion than on established facts. I don't think a decision as to which method is best can be made at present. We have continued to use interrupted cortisone therapy because this method of giving cortisone has seemed fairly effective, and because of the theoretical advantage that less adrenal suppression might occur if the patient is off cortisone for four days between courses of therapy.

DR. WALLACE MCCRORY, Iowa City: I would like to commend Dr. Worthen for focusing our attention on a problem all of us would like an answer to. The interval between observed relapses in patients with nephrosis has been a subject of interest for some time. Some writers have applied the term "polycyclic nephrotic syndrome" to such patients when they have long intervals of apparent good health between relapses. The question of basic importance here is whether such patients represent instances of recurrence or of new attacks. In the experience gained in Philadelphia, it appeared that the pattern of the early course of the patient following initial steroid treatment was at times of great help. We found those patients who responded to initial therapy with complete remission and remained in remission for at least three months following such treatment, all have continued with a benign course in a three- to four-year follow-up, even though many of them have subsequently had recurrences. I believe it would be most important to have some knowledge of the severity of the disease early in the course of therapy in studies dealing with analyses of subsequent pattern of patients' behavior.

DR. WORTHEN: I would agree that the response of the patient to the initial course of therapy is a good index of prognosis, and probably a better prognostic sign that any of the usual function studies. In our experience, the patients who failed to respond to the initial therapy have generally had a poorer outlook than those who responded well. The excellent response to re-treatment in the patients presented today was encouraging, and indicated to us that the ultimate prognosis in these patients was probably good in spite of the relapses.

DR. MILTON RAPOPORT, Philadelphia: I was going to make a comment prior to Dr. Butler's questioning the relative merits of intermittent versus continual steroid therapy. I'd like to provide a little more confusion by saying that I have the impression that there is definite demerit in the intermittent therapy. This was first brought out by a 15-year-old girl who is a gifted student and a gifted mathematician who is doing advanced calculus in about the third year of high school. On the days when she takes steroid, she can do her calculus; on the days when the steroid is withdrawn, she flunks way back to long division. About the third day of withdrawal, her family can't live with her because she is so hysterical. With this observation, if you start looking a little more closely at the behavior of your patients rather than at what their urine is doing or at whether they're showing any physiological or biochemical changes due to giving steroid intermittently, I think you will find that a fair number of children have cyclic bad behavior, and that it takes a day of steroid to restore them to what their base-line behavior is, and that when it is stopped, they get more or less agitated and difficult to live with after the first day of withdrawal. This is not true of the youngest ones. In young children it's pretty hard to tell what the basic behavior is. But the older children who have more or less fixed patterns get quite disturbed. If you make some inquiries, you will find out that they are hard to live with and that they can't do any school work. All sorts of things happen to them behaviorwise. I have never been quite convinced about any real basis for giving steroid for three or four days and then stopping it for three days. I am convinced that if you take the same dosage and spread it over seven days you will accomplish as much or as little as you would with the other way of giving medication.

Relative to Dr. McCrory's statement, I now have one child who has had a recurrence who was the first patient we ever treated with corticotropin (ACTH) in 1949. She was completely free of symptoms and laboratory findings and everything else for a 10-year period but has now had a full recurrence of her nephrosis. Certainly in 10 years she must have had a lot of antigenic stimulation, and what was it that set her off after 10 years' interval?

We have another youngster who never received steroid who had a recurrence after 11 years, and a third youngster who had been completely well for 5½ years and who immediately after a tonsillectomy had a full recurrence lasting four months.

There are patients whose symptoms recur who have benign disease. I think Dr. Kohn collected a number of these who were adults. Among them is a woman who still continues to have proteinuria at age 39 after having had three children. These

patients do not have the lethal kind of disease and we haven't yet separated out all such patients. I think we ought to be a little cautious about generalizing on the prognostic significance of a patient who relapses. Apparently children have a tough enough time without our introducing this as another prognostic criterion.

DR. DONALD GRIBETZ, New York: In relation to the comments of Dr. McKay, we too have been intrigued with the observation of the frequency of edematous recurrences in our nephrotic children during the summer months. During the past four to five years, we had the impression that a high percentage of exacerbations in these children has occurred during July and August. We initially presumed that this may have had some relationship to sweat electrolytes or to adrenal function. Lately, Dr. Horace Hodes has attempted to stimulate us along the lines mentioned by Dr. McKay, i. e., to look into the possibility of a viral etiology for this phenomenon.

The question I would like to put to Dr. Worthen is as follows. Have you had any follow-up of children who have been edema-free for three or four years? We had thought, based on studies of our own series, that children who were clinically "well" for four years after an edematous episode could be considered "cured" of the disease. Our confidence concerning this point is now being shaken, however, since, as has been pointed out, exceptions after this period of four years are appearing.

DR. HOWARD G. WORTHEN: Dr. Gribetz, we haven't followed any patients who have gone as long as three or four years before relapse, so we can't give you any information on how many relapses might occur that long after therapy.

DR. ROBERT J. MCKAY, Burlington, Vt.: To confuse Dr. Rapoport further and to prove that patients are still individuals, we have one patient whom we would like to keep on continuous steroid therapy but cannot because he becomes unbearable from the behavior standpoint when he is on it.

11. Production of Nephrotic Syndrome in Rats by Sensitization to Rat Kidney Proteins

WALTER HEYMANN, M.D.; DONALD B. HACKEL, M.D.,* and JANET L. P. HUNTER, M.R.C.P., E.* Department of Pediatrics, Western Reserve University School of Medicine, Cleveland.

Even though heteronephrotoxic antibodies have been shown to induce the nephrotic syndrome in rats, it has thus far not been possible to produce nephrotic renal disease experimentally by iso- or autosensitization to kidney proteins. The following studies suggest this immunochemical process as the underlying pathogenetic mechanism.

Rats were given 0.25 ml. of a mixture consisting of 1.0 ml. of Freund's adjuvants and 0.4 ml. of a low-speed supernate of a 1:1 rat kidney suspension, by intraperitoneal injection every two weeks. Each injection contained 2 to 2.5 mg., or less, of tissue protein. After two to six injections all 25 so-treated animals developed marked proteinuria, hypoalbuminemia, hyperlipemia, and characteristic histological lesions in the kidneys. When liver tissue was used, a much less marked nephrotic syndrome was noted in only 2 of 15 rats. None of the 20 animals treated with adjuvants alone, or with adjuvants and lung or muscle tissue suspensions developed proteinuria.

Unilateral nephrectomy was performed in seven rats. Four to thirteen weeks later they were injected according to similar schedules with Freund's adjuvants and a low-speed supernate of a 25% suspension of their own, previously removed, kidney tissue. Severe nephrotic renal disease was noted in five of the seven animals so treated. Using Ouchterlony's technique of double diffusion in agar plates, 132 sera obtained from 54 of these rats were studied for observation of bands of precipitation. When the same antigen was used, as was used to elicit renal disease, well-defined zones of precipitation were noted one to four weeks prior to the onset of proteinuria and persisted for one to eight weeks, even though renal disease continued for months thereafter. A study for complement activity was made of 133 sera obtained from 48 rats. A sudden decrease of complement activity was noted that coincided with the onset of proteinuria and succeeded the appearance of bands of precipitation in the sera by several weeks.

Discussion

DR. VINCENT C. KELLEY, Seattle, Wash.: In the rats in which the microscopic changes and proteinuria were produced with Freund's adjuvant alone, did you also try the precipitin reaction?

* By invitation.

DR. WALTER HEYMANN: We studied two groups of rats; one group received 0.25 cc. and the other group received 0.5 cc. of Freund's adjuvants without added tissue proteins. Marked proteinuria was observed only in some of those that were given the larger amounts of adjuvants. Bands of precipitation in sera were not observed in any of the rats that received 0.25 cc. of the adjuvants alone. Sera of rats treated with 0.5 cc. of adjuvants without tissue suspensions have not been tested for bands of precipitation as yet.

DR. HORACE L. HODES, New York: I'd like to ask Dr. Heymann one question or make a suggestion about one thing. I think he showed very clearly with the Ouchterlony technique that an antibody rise occurs. I wonder whether this reaches a peak and then goes down?

In light of the discussion of the last paper, I wonder what would happen if, after a fall in antibody, you then, at a later date, gave adjuvant alone. Would one get a rise again in the precipitin antibody?

Also you might try stressful situations such as subjecting the rats to heat, cold, forced work, and so on. It seems to me that you have a model that might cast some light on the discussion that went on after the preceding paper. However, as you say, this is not necessarily a human disease.

One technical question, how long did it take for the precipitin band to show up?

DR. HEYMANN: Thank you, Dr. Hodes, for your very good suggestions. We have, as yet, not performed any of your suggested experiments. Since we are in the primary stage of the study, I am sure that we will go into many of the problems you suggested at a later date.

Bands of precipitation become visible after two to four days if the wells are kept 1 cm. apart. If one leaves the plates a few days longer, the bands become even more distinct, and after three to four weeks they may become thick.

DR. RICHARD T. SMITH, Gainesville, Fla.: These studies appear to be an excellent demonstration for the first time of autoimmunity as an experimental model for renal disease. I admire Dr. Heymann's reluctance to implicate immunological mechanisms as the direct cause of the disease he sees. In the past, the same reluctance has not always been shown at the meetings of this Society. His conservatism is very well justified.

Dr. Heymann, did you attempt to elicit a secondary response, which, according to immunological principles, not only should require less antigen, but should occur more immediately, perhaps after a single injection?

Have you tried to inject kidney extract during the neonatal period? Rats are excellent animals in which to produce immunological tolerance, and it would be very interesting to attempt to produce tolerance in rats, using your model.

DR. HEYMANN: I must restate that we were so busy observing and accumulating data on the primary disease, that provoking challenges at a later date have not yet been attempted. The possibility of preventing this experimental disease by inducing immunological tolerance in the newborn animal is on our list of "things to be done." I believe that Dr. Calcagno from Buffalo has accumulated some data about a similar problem in relation to nephrotoxic serum disease in rats.

DR. KURT LANGE, New York: The beautiful and elegant experiments of Dr. Heymann are a decisive step forward in the direction of elucidating the mechanism of human glomerulonephritis by experimental models. The only question is whether or not the use of Freund's adjuvant does not mar the picture. If Freund's adjuvant were just an amplifier of immunologic response, then one would think that correspondingly larger doses of kidney antigen alone should also be able to produce an identical reaction, and I would like to ask Dr. Heymann whether this is the case or not. In addition, I would like to ask Dr. Heymann whether or not Freund's adjuvant without killed tubercule bacilli was used and, if so, what the reaction was?

If Freund's adjuvant is indispensable in obtaining the reaction, then one could think that Freund's adjuvant breaks down some of the kidney tissue by localization on the kidney and that this localization is directed to the kidney by the combination with kidney substance. Subsequent to the breakdown of the kidney tissue, a secondary antibody is formed by the animal itself against the kidney protein.

This would be comparable to the findings which we published in 1949 and which were confirmed by Dr. McCrory and his group and by other groups here and in Europe, that in cases of human patients with glomerulonephritis antibodies against kidney can be discovered with sensitive techniques. All students of this problem seem to agree that these antibodies are absent in the first days or weeks of acute glomerulonephritis and appear only later when the disease has already passed its most acute stages. We now feel that we are probably dealing here with a secondary antibody to kidney after destruction of kidney tissue has already taken place due to the immune reaction between some streptococcal products and their respective antibodies.

DR. HEYMANN: In answer to Dr. Lange's first question: I may quote that we have tried kidney suspensions alone, without adjuvants, given by intraperitoneal injections, in larger amounts, without ever observing resulting proteinuria. This also supports our belief that the subclinical injury to

the kidney induced by adjuvants alone may be an important pathogenetic factor. This problem is open to further experimental approach, and we had better wait for these observations before going into far-reaching hypothetical considerations.

I may assume that it is of interest to the audience to know that we naturally jumped at the sera that we have been saving for years. These sera were obtained from children with a fresh, two- to three-week old, and as yet untreated nephrotic renal disease. We have used the same agar plate technique with all sorts of antigens—crude ones and high speed supernates of freshly obtained human kidneys—and we have, thus far, failed to observe any lines of precipitation or titers of agglutination using Boyden's hemagglutination technique.

Dr. Robert Blizzard, Columbus, Ohio: I would like to ask what the histology of the liver was secondary to the various injections?

Dr. Heymann: This poses the question as to whether the observed liver antibodies produce liver disease or not. Apparently, they do not. Dr. Hackel has done the pathological studies on these slides and assured me that he has not seen any changes in liver tissue as yet.

Dr. Philip L. Calcagno, Buffalo: Both Dr. Rubin and I have been interested in this problem of specific renal antigenicity, but we have performed most of our experiments in the newborn period of small rats.

We found that when we injected small rats with nephrotoxic serum within zero to three hours after birth, we were not able to produce the nephrotic syndrome in these animals even when they were allowed to grow to maturity. Clinically there was no proteinuria, no edema, no biochemical change, and no pathological changes were observed with light microscopy. This finding was even more intriguing when we were able by fluorescent antibody technique to demonstrate the antibody attached to the glomeruli one day after birth (or 21 hours after the injection). However, when we gave the newborn rat 0.5 cc. of a 20% suspension of kidney extract subcutaneously, we found that these animals who were small, had proteinuria (2 to 3 mg/hour), hypercholesterolemia, and pathological examination by light microscopy revealed extensive chronic glomerulonephritic changes. So it would seem to us that the young animal apparently doesn't respond to nephrotoxic serum, or that there is some tolerance to nephrotoxic serum in the early newborn period. This does not appear to be true with the kidney antigen, and I think that in this phase of our experiments the data are comparable to those of Dr. Heymann.

Now I should like to ask one question of Dr. Heymann. I was a little surprised to see that the lung injection didn't show anything, since lung tissue can absorb out kidney antibody perhaps better than liver, and I would have anticipated that lung would have produced some disease. I wonder if Dr. Heymann has some explanation for this?

Dr. Heymann: I do not have an explanation and also have anticipated that lung, rather than liver, would give rise to an occasional and not too severe renal disease. The concentration of proteins in our lung tissue suspension was lower than in kidney suspension, but not low enough to explain the completely negative results.

Dr. Robert J. Slater, Toronto, Canada: I am interested to know if it might be possible to differentiate the influence of the adjuvant and the kidney antigen in the experimental animal. Have you taken the serum from the animals after they have been immunized and are suffering from the "autoimmune" disease and then injected it into an untreated rat to see what would happen? This might reveal a difference between the response of an animal who has received Freund adjuvant in contrast to one who has not, with regard to the reactivity of the kidney to circulating homologous antiserum.

Dr. Heymann: This work progressed so well that we always were fearful of meeting our Waterloo somewhere. We met our Waterloo when we tried to inject healthy rats with serum or ascitic fluid obtained from rats that had the induced disease. No proteinuria was noted in the recipients. I have learned, however, that the transmissibility of any of the experimental autoimmune diseases is difficult to achieve. At this year's Federation Meetings (held in Atlantic City three weeks ago), the transmissibility of so-called allergic encephalomyelitis was, however, reported. We are continuing the work on this problem and believe that the failure to transmit this disease by injecting sera or ascitic fluid does not mean too much. The actual amount of antibodies so transferred may well be too small.

Dr. John L. Sever, Evanston, Ill.: For several years a group of investigators at Northwestern University has been studying the application of the Ouchterlony reaction plate technique to the problem of antigenic relationships between Mycobacteria. They have recently reported that several bands of precipitate appear with this technique when serum from tuberculin-positive persons or experimental animals is tested. In view of this relation between bands of precipitate and tubercle bacilli, and since Dr. Heymann employs an adjuvant which contains tubercle bacilli, I wonder if he has conducted any investigations to rule out the tubercle bacilli as the source of the antigens to which the bands relate.

Dr. Heymann: We have not done that. I should state, however, that bands of precipitation

obtained with sera of adjuvant-, kidney-, or liver-treated animals all showed one single band, whereas nephrotoxic sera obtained from rabbits against rat kidney all gave three to five bands. I do not believe that the lines of precipitation obtained in sera of adjuvant-, kidney-, or liver-treated rats is due to the incorporation of killed tubercle bacilli, because sera of rats treated with adjuvants alone (which contain the same amount of killed tubercle bacilli) never gave us lines of precipitation.

12, Chorioretinitis and Central Nervous System Diseases in Infancy. RICHARD J. ALLEN, M.D.,* and JAMES L. WILSON, M.D. Department of Pediatrics and Communicable Diseases, University Hospital, Ann Arbor, Mich.

In the past two years 10 infants have been seen in the Department of Pediatrics, University of Michigan Hospital, varying in age from 2 weeks to 26 months, with chorioretinitis and severe central nervous system diseases. There are in addition certain uniform clinical characteristics: 1. Skull x-rays in every infant have failed to reveal any intracranial calcium. 2. All the infants had toxoplasma tests and most had other tests for the commonly considered infectious diseases with negative results. 3. The family history for any similar disorder was negative in each instance, and the 19 living siblings of these 10 patients are unaffected.

Although many etiologies must be considered when chorioretinitis is found in an infant, in the absence of intracranial calcium and negative toxoplasma tests, few causes are identified. Chorioretinitis with intracranial calcium and central nervous system abnormalities (hydrocephalus, microcephalus, severe mental retardation, etc.) is generally considered to be due to toxoplasmosis; however, the serological tests often identify patients with similar symptoms but presumably not due to this organism. The accompanying table contains the major groups of infants with chorioretinitis reported in recent years.

One of the largest groups of infants with chorioretinitis and central nervous system disease not due to toxoplasmosis was reported by Sabin in 1949 (Group III). It is interesting to note that 5 infants were from England and Holland, while the remaining 14 were from nine different states in the U. S. A. Scattered reports have appeared since of a few similar cases, but no common etiology has been found. Cytomegalic inclusion body disease may also be associated with intracranial calcium and central nervous system disease but in only two such cases has chorioretinitis been reported (Group IV).

Our group (Group V) of infants is unusual in that this is the largest series to be identified in a single locality with chorioretinitis and central nervous system disease in the absence of positive toxoplasma tests. Also, preliminary information is available on one infant and tissue cultures of intraventricular fluid suggests that a cytopathogenic agent is present. A brain biopsy on this infant reveals definite architectural changes (maldevelopment of cortex) associated with perivascular, subependymal accumulations of calcium and cells. It would appear that the absence of intracranial calcium on skull x-rays can not be used as a differential point in separating these groups. Also, the identification of a filtrable cytopathogenic agent from the in-

* By invitation.

Classification of Infants with Chorioretinitis

Group	Chorioretinitis	Intracranial Calcium (X-Rays)	Toxoplasma Serological Tests	Cytomegalic Inclusion Bodies	Viral Studies	Authors
I	+	+ (92%)	+			Wolf, et al., Sabin
II	+	+	0	?	?	Sabin, Wyatt
III	+	0	0	?	?	Sabin
IV	+	+	0	+	+	Weller, Guyton
V	+	0	0	0	+	Allen, Wilson

traventricular cerebral spinal fluid may relate this group to one or more of the others when our studies are completed.

Discussion

DR. ALFRED FLORMAN, Manhasset, N. Y.: I agree with Dr. Allen that the syndrome of chorioretinitis and severe central nervous system disease may occur in association with infections other than toxoplasmosis. Some years ago Dr. Mindlin and I had an opportunity to study and report triplets, (A. M. A. AM. J. DIS. CHILD. 83:481-486, 1952), one of whom developed postnatally severe generalized herpes simplex. This resulted in chorioretinitis and gross cerebral damage without evidence of cerebral calcification. Herpes simplex is therefore another infectious agent which may lead to this syndrome.

DR. SAMUEL L. KATZ, Boston, Mass.: Dr. Allen, I don't understand two points in your discussion. First, have studies been done with the agent which you isolated to determine if it is identical with the virus responsible for cytomegalic inclusion disease? Have you done any serological studies in any of your other cases to rule this same etiological agent in or out? In regard to chorioretinitis, I think it is now well established that patients with cytomegalic inclusion disease may often manifest this same feature. Dr. Thomas Weller has told us that three of his nine virologically proved cases have chorioretinitis.

DR. RICHARD J. ALLEN: There are probably many unreported cases of chorioretinitis associated with cytomegalic inclusion disease. However, to my knowledge there are only two definite reports associating retinal changes with cytomegalic inclusion disease, but in these infants there was in addition, periventricular calcium evident on skull x-rays and a history of generalized systemic disease in early infancy compatible with this diagnosis.

Our infants had chorioretinitis with central nervous system involvement, but there was no x-ray evidence of intracranial calcium and in only one was a history of jaundice in early infancy present. Therefore, on a clinical basis, in the absence of toxoplasma antibodies, the etiology would be obscure. However, our studies in the last infant resulted in the isolation of an unidentified virus from the intraventricular fluid to which this infant and three others in the series demonstrated antibodies.

We are unable to state as yet whether this agent is definitely related to the salivary gland virus, although there are some similarities. Several syndromes of chorioretinitis are recognized in infants, but when definitive methods of diagnosis are better understood, possibly a relationship will be evident between some of them.

13. Relation of Intracellular Ions to Metabolite Sequences in Kwashiorkor.

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Kwashiorkor (severe protein and calorie malnutrition) is a major cause of death in children of technically underdeveloped areas of the world. Previous studies demonstrated profound hypotonicity and biochemical distortion of the body fluids. Increased $(H_2O)_{icw}$ and $(Na)_{icw}$ with reduced $[K]_{icw}$ but without significant depletion of $(K)_{icw}$, characterized intracellular fluids (( )=content, [ ]=concentration, icw=intracellular water). It was thought that decreased $[K]_{icw}$ might affect some electrolyte-dependent cellular metabolic sequences, thus reducing energy yields required for Na extrusion.

To explore this hypothesis, initial and repeat muscle biopsies were obtained from eight children with severe kwashiorkor. Three died subsequently. Cell electrolytes were measured, including Mg, total (P_T), "apparent" inorganic (P'_i) = phosphocreatine + "true" inorganic P (P_i), and "organic" phosphate $(P_o)=(P_T-P'_i)$. Non-collagen nitrogen (NCN), terminal metabolites of the Embden-Meyerhoff pathway, pyruvate and lactate, and two components of the citric acid cycle, citrate and α-ketoglutarate, also were determined. Interrelationships of these components, adjusted for (NCN), were expressed as ratios.

In children who died, cellular ratios of $\left(\frac{\text{lactate}}{\text{pyruvate}}\right)$, $\left(\frac{\text{citrate}}{\text{pyruvate}}\right)$, and $\left(\frac{\text{citrate}}{\alpha\text{-ketoglutarate}}\right)$, increased, although $\left(\frac{\text{citrate}}{\text{NCN}}\right)$ was unaltered. With reference to electrolytes, decreased $[K]_{icw}$ and $(P_T)_{icw}$, with increased $(P'_i)_{icw}$ relative to $(P_o)_{icw}$ were found in

* By invitation.

all malnourished children. $\left(\frac{(P_o)}{\text{pyruvate}}\right)$ ratios decreased, while $\left(\frac{(Na)_{lcw}}{\text{pyruvate}}\right)$, $\left(\frac{(P_i)}{\text{pyruvate}}\right)$ and $\left(\frac{(P_i)}{\alpha\text{-ketoglutarate}}\right)$ increased markedly in children who died.

In-vivo data facilitating interpretation of these observations are not available. In-vitro studies indicate that, ordinarily, metabolism of α-ketoglutarate via succinate should decrease $\left(\frac{\text{citrate}}{\alpha\text{-ketoglutarate}}\right)$ and especially $\left(\frac{(P_i)}{\alpha\text{-ketoglutarate}}\right)$; however, both ratios increased in children who died. Since α-ketoglutarate decreased but neither disappearance of (P_i) characterizing succinate formation, nor accumulation of citrate or pyruvate was found, production of α-ketoglutarate might have been limited and/or Krebs' cycle metabolism could have proceeded by transamination, for example, via pathways favoring abnormal amino acid metabolism or lipogenesis, perhaps reflected in the unusual amino acid patterns, fatty livers, and conservation of subcutaneous fat, despite gross caloric deficiency, observed in progressive kwashiorkor.

The alterations of intracellular Na, K, Mg, and apparent inorganic (?high-energy bond) P relative to pyruvate are consistent with failure of the energy-generating dephosphorylation of phosphoenolpyruvate which in-vitro partially depends on $[Mg]_{lcw}$ and $[K]_{lcw}$. Since increased $[Na]_{lcw}$ acts as a specific inhibitor in the system, (in vitro) substrate cofactors would be expected to accumulate. Relative to pyruvate, $(K)_{lcw}$ and $(Mg)_{lcw}$ approximately doubled, although quantities per gram NCN were only slightly altered in children who died.

Whether such ratios are valid or whether the data can be interpreted as described is not known. The limitations of technique and interpretation are recognized; nevertheless distortion of intracellular ion contents assumes new significance when expressed as a function of some related, dynamic component of cell metabolism. These interpretations clearly require further investigations, for they imply (1) that some aberration in the final common pathway of cellular metabolism related to α-ketoglutarate may characterize the amino acid and lipid disorders; and (2) decreased phosphopyruvic kinase activity and/or diminished utilization of inorganic (?high-energy bond) phosphate accompanies reduced $[K]_{lcw}$ with accumulation of Na and H_2O intracellularly, initiating an irreversible clinical state causing death from kwashiorkor.

Discussion

DR. LAURENCE FINBERG, Baltimore: What is the influence of death on the muscle concentration of the various organic constituents you have measured? Have you examined muscles for these constituents in patients who have died from causes other than kwashiorkor?

DR. JACK METCOFF: We have had an opportunity to do this only in premature infants and have now studied about six babies. Two muscle biopsies were taken from the same baby at 5- to 10-minute intervals after death, in order to determine whether there were changes in metabolite concentrations. We found no significant differences within about the first five minutes after death, with the exception of lactate, which increased. In these biopsies the values for pyruvate and alpha ketoglutarate in the premature infants were of the same order of magnitude as the inital biopsies in the kwashiorkor patients. They were generally higher than the comparable final biopsies in the patients who died of kwashiorkor. When data are available for otherwise normal children, we will have a better appreciation of the variations of organic constituents. There are not sufficient human data available. There is some evidence that the adenine nucleotides, respiratory enzymes, and actomyosin contractile responses in heart muscle remain unchanged for at least one to two hours after death.

DR. SOLOMON A. KAPLAN, Los Angeles: This is a syndrome of protein malnutrition, and it must be remembered that cell enzymes constitute the major fraction of cellular proteins. I should like to ask Dr. Metcoff if alterations in intermediary metabolism could be ascribed to general deficiencies in enzyme proteins and cofactors instead of being part of the disease process.

DR. METCOFF: This is a very good question, Dr. Kaplan. The problem is a real one. First of all, how much enzyme is "enough" within a cell to produce the desired rate of enzymatic transformation?

As far as I know, this has not been defined. Drs. Waterlow and Scrimshaw and their associates have attempted to study enzyme concentrations in muscle and liver, respectively, of kwashiorkor patients. With the exception of two enzyme systems that I can recall, D-amino acid oxidase and xanthine oxidase, no abnormalities were demonstrated in the enzymatic concentrations in these tissues, suggesting that the enzyme per se may not be deficient.

This would be consistent with the fact that the noncollagen nitrogen content per 100 gm. of dry fat-free of surviving muscle appears to be at least normal in children with kwashiorkor.

We think that there is a kind of cannibalization which occurs, since muscles which degenerate as a result of inadequate nutrition presumably contribute their quantity of cellular content to the general body pool and thus sustain the activity and composition of the residual muscles.

DR. ROBERT E. COOKE, Baltimore: I think there is one other question which I'm sure the speaker is aware of, namely, that the whole tissue analysis may not well represent changes in certain subcellular fractions. There may be an electrolyte environment for particular enzymes which is very different from what would be reflected in the whole cell analysis. I simply mention this to point out the difficulties, not the shortcomings, in this kind of work.

DR. METCOFF: I can only say "amen."

DR. NATHAN TALBOT, Boston: Another factor which I think may come into play under circumstances of this sort is that of changes due to circulatory inadequacy. I wonder whether these patients of yours died slowly?

DR. METCOFF: Dr. Talbot, my own experience with kwashiorkor is extremely limited, but I have seen these particular youngsters die and my colleagues in Mexico inform me that one of the characteristic features of death in kwashiorkor is that it is not only sudden but often unpredictable. For example, during our rounds examination of one child indicated that all seemed to be well and we passed on to the next bed, but a few minutes later, when we turned around we discovered that the child had died. Death sometimes occurs this rapidly. Usually death is not a protracted affair in this kind of severe kwashiorkor. I think perhaps some of my colleagues from Mexico who are here might care to supplement my comment.

DR. G. MISRA, India: Clinically skin and hair changes similar to those in kwashiorkor have been observed in cases of the "malnutrition syndrome." Respiratory complications and biochemical disturbances are important causes of death in this syndrome, but it is also felt that vitamin B_1 deficiency and adrenocortical insufficiency are contributing factors. Unfortunately, our lack of laboratory facilities has prevented us from proving this conclusively.

May I have your thoughts on these remarks?

DR. METCOFF: It's very difficult to answer these questions precisely except to repeat a little of the experience of others. I have no firsthand experience with either B_1 deficiency or possible deficit in adrenal cortical activity. Dr. Gomez's group have systematically explored potential vitamin deficiencies in the Mexican children whom they have studied and I believe have not found significant vitamin deficiency, specifically no B_1 deficiency in these children. This may not reflect the situation in India, for there is a considerable difference in the daily dietary pattern, since Mexican children subsist primarily on corn whereas the Indian children subsist on rice.

As far as adrenal cortical deficiency is concerned, the few studies that I know of have not demonstrated deficits in the excretion of adrenal cortical intermediates, suggesting that there is no failure in production or lack of the adrenal cortical steroids.

DR. DANIEL DARROW, Mission, Kan.: While I was riding with Dr. Metcoff from Atlantic City, he pointed out that total tissue sodium and potassium would account for a greater osmotic pressure than that of serum. The previous observations indicated that shifts of water occurred when serum sodium concentrations altered. Consequently osmotic equilibrium is presumably maintained between extracellular and intracellular fluids. Has Dr. Metcoff any speculations on these observations?

DR. METCOFF: I knew I should never have mentioned that to you.

It is quite true that the tissue analyses, irrespective of the assigned position of chlorides, indicate that the concentrations of intracellular sodium and potassium are much greater than can be accounted for on the basis of their extracellular fluid concentrations. This is not only characteristic of our studies; it seems to occur in many others as well. Any attempts to explain this would be sheer speculation with the data obtainable. We unfortunately have no measurement of the potential of water across the membrane. If the potential of water were the same on both sides of the membrane, extracellularly and intracellularly, then one would have to assume from our measurements that some of the excess sodium and probably some of the potassium were inactivated by existing in some form of intracellular complex, presumably with the protein or other anionic component within the cell. This is a very unpleasant prospect to consider, but I know of no other way to explain it.

14. The Effect of Potassium Supplementation of Wheat in the Diets of Infants.

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Vegetable proteins, particularly wheat, were evaluated as sources of nitrogen for the human infant by balance techniques. Twenty-two malnourished male infants aged 3 to 17 months were studied for periods of 27 to 54 days on diets of wheat or wheat-milk mixtures.

The biological value of wheat protein as measured by nitrogen balances was found to be increased by the addition of potassium and to be further increased by the addition of small amounts of lysine. Infants were fed 1.2 to 4.0 gm. of protein/kg/day and 75 to 120 calories/kg/day. Adequate retentions were found when 2.0 gm. of protein, whether animal or vegetable, and 100 calories per kg. were fed. Potassium was added to provide a total intake of approximately 3 mEq/kg/day, and the wheat was supplemented with lysine to yield a total concentration of 0.45% lysine. Protein retention of lysine- and potassium-supplemented wheat protein became approximately equal to that of milk protein.

It has long been known that adequate potassium is essential for protein retention. It is also known that children with kwashiorkor present with potassium deficiency. The present communication may indicate that in those areas in which vegetable proteins constitute the main protein source, the biological usefulness of protein may be increased by addition of such simple minerals as potassium.

Discussion

DR. JOAQUIN CRAVIOTO, Mexico. I would like to comment that practically all cases of chronic severe malnutrition present potassium depletion, and this potassium depletion is caused in the majority of them by lack of intake. These patients when coming to a hospital have been sometimes for several weeks on a diet composed almost only of carbohydrates with practically no potassium intake at all. The losses through diarrhea, although also very common, do not, in our experience, constitute the main reason for the potassium deficiency.

I would like to ask what could be the explanation for the differences in response of the children, since some of them increase their nitrogen retention while others decrease it, and there are some who showed no change in the magnitude of the balance. Is there a difference in the age of the children or in the dietary history?

The other point is that in supplementing a diet of corn and beans with lysine, we have followed the amino acid excretion in the urine and we have one case who showed a greater excretion of valine during the supplementary period, so for all this, we would like to consider that before going into the practical aspects of suggesting a supplementation of lysine to a poor diet for human consumption purposes, it should be clear that no amino acid imbalance is being produced by the addition of the supplement.

DR. AREE VALYASEVI: I think your first question refers to two babies in whom no increase in nitrogen retention was consistently obtained when wheat was supplemented with potassium and lysine. The supplemental potassium was given by mouth once daily to one of these two babies. For the rest of the subjects the potassium was mixed in the formula, and the consistent beneficial effect of potassium and lysine supplementation was obtained except in one baby whom you also refer to. This baby had a remarkable nitrogen retention throughout the period of study. We feel that supplemental lysine and potassium should be mixed thoroughly with the daily diet.

We were also aware of the amino acid imbalance. However, it is pretty well established in rats that lysine is probably the only limiting amino acid in wheat. As far as we can tell by nitrogen balance technique, there is no indication of amino acid imbalance when lysine was supplemented in the amount to yield 0.45% of total intake.

DR. JACK METCOFF, Chicago: I wonder if you would be good enough to tell us, first, what the potassium to nitrogen ratios were in relation to the changing supplementation period? As I gather, roughly, from your slide, the potassium to nitrogen ration is not always consistent with a specific effect of either potassium or lysine supplement. Secondly, how were the variations in body weight correlated with changing balances of potassium to nitrogen? It seemed that in some of the balance studies

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weight loss characterized periods when there was a maximum gain in both potassium and nitrogen.

DR. VALYASEVI: The potassium to nitrogen ratio ranges from 1:1 to 5:1; mostly it is between 2:1 and 3:1.

Regarding your question about the correlation between the weight changes and the nitrogen balances—in our experience, the weight changes have very little value in a short-term study. A few babies, not included in the series present today, had not gained good weight and even lost some in spite of good nitrogen retention on milk diet. Furthermore, we have observed that many babies had not gained weight for a period of one to two weeks after resuming a regular high-quality diet after the balance study was completed.

DR. MOISES BEHAR, Guatemala: At the Institute of Nutrition of Central America and Panama (INCAP), we have been studying, by the metabolic balance technique, the effect of supplementation of cereals with amino acids.

We have found that when corn proteins are supplemented with their deficient essential amino acids, in the amounts required to match the amino acid pattern or "reference protein" of the Food and Agricultural Organization (FAO), the nitrogen retention is equal to that observed with milk at the same nitrogen and caloric intake, when tryptophane, lysine, and isoleucine are added.

In the case of wheat, the same results can be obtained with lysine supplementation alone. Our experimental subjects have been children 1 to 4 years of age, who were also malnourished upon admission to the hospital, presenting severe protein deficiency as well as potassium deficiency. However, the balances were not initiated before a complete clinical recovery was observed, that is, at least after three months of adequate dietary treatment. I wonder if in the cases studied by you the patients were still deficient in potassium when the balances began; that might explain the effect of potassium.

DR. VALYASEVI: Our subjects were only underweight. They were not severe malnutrition cases.

We were also aware of this possibility. Our potassium balance data does not support this possibility because there is no more potassium retention in the early than the later parts of the study.

15. Histidine, an Essential Amino Acid for the Infant. SELMA E. SNYDERMAN, M.D.*; PHILIP H. PROSE, M.D.,* and L. EMMETT HOLT JR., M.D. With technical assistance of ELLEN ROITMAN, A.M.* and AUDREY BOYER, B.S.* Departments of Pediatrics and Pathology, New York University College of Medicine, New York.

This study was undertaken to determine if histidine is a dietary essential for the infant. Although it is a growth requirement of several animal species (rat, dog, mouse, chick, pig), adult man can maintain weight and nitrogen equilibrium in its absence. A synthetic diet was used, the protein moiety of which was a mixture of 18 L-amino acids in the proportion found in breast milk. After a control period, the histidine was completely withdrawn from the diet. The nitrogen intake was kept constant at all times by the substitution of glycine. The subjects were eight normal male infants who ranged in age from 2 weeks to 7 months, and the period of histidine withdrawal was from 1 to 3 weeks.

Histidine withdrawal resulted in either complete cessation of weight gain or very poor weight gain in all of these infants. It was accompanied by impairment of nitrogen retention in six infants. Quantitative determination of the free amino acids of the plasma by column chromatography performed in four subjects revealed a decrease in histidine as the only consistent change. The urinary excretion of histidine tended to fluctuate with the intake in the two subjects in which it was measured.

Of particular interest was the appearance of a specific clinical symptom of histidine deficiency. This was a very scaly rash on an erythematous base that had an appearance similar to infantile eczema. However, there was never any associated pruritus. It appeared within 5 to 8 days after histidine was withdrawn and started to improve 48 hours after histidine was reintroduced into the diet. The occurrence of the rash may be related to the age of the infant since it appeared in five of the six subjects under 2 months of age but in neither of the two subjects over 7 months. Biopsy specimens from the involved skin of the face of two of these infants were examined. The pertinent findings included parakeratosis and minimal acanthosis, and throughout the

* By invitation.

corium there were dilated capillaries lined by plump endothelial cells and pronounced perivascular edema. Acid mucopolysaccharides were abundant at the junction of the dermis and the subcutaneous fat, and glycogen was found within the fat cells of the subcutis. There were several sites where alkaline phosphatase activity could be determined histochemically.

An attempt was made to determine the histidine requirement by its gradual reintroduction into the diet of six infants. When 33 mg/kg/day was given all gained weight at the same rate and retained as much nitrogen as they did while receiving the control diet. Only one child had a good performance on 22 mg/kg/day. Hence, the infant requirement for histidine lies between these two figures.

Discussion

DR. DONOUGH O'BRIEN, Denver: We have been impressed by the apparently precarious conservancy of histidine on the basis of calculated figures for intake in comparison with other essential amino acids. The mean excretion at 6 weeks in our group of 11 premature infants was about 80 micromols per kilogram per 24 hours, with a very wide scatter not entirely related to nitrogen and histidine intake. From your figures I would calculate that requirements are of the order of 160 μM/kg/24 hours, a much narrower margin than for other essential amino acids. I wonder, therefore, if you would accept that some part of the essentialness of histidine is related to sparsity in the diet rather than to any immaturity of synthesis.

DR. SELMA E. SNYDERMAN: I do not believe we have the answer to that. We certainly have seen a difference in histidine excretion in the urine when there is a controlled intake, and we also have seen the variations of plasma concentration of histidine which is also dependent on the intake.

DR. H. DAVID MOSIER, Los Angeles: One would suppose that if the infants were deficient in histidine they might not be able to make normal thyroglobulin. In connection with this point, I wonder if perhaps thyroid deficiency played a role in the growth failure of your cases and whether you have assessed thyroid function?

A second point is that an eczematous rash can be seen in phenylketonuria, which is another amino acid disturbance. Have you considered the possible relationship of the rash in this amino acid disturbance with that of phenylketonuria?

DR. SNYDERMAN: We saw nothing clinically to suggest thyroid deficiency. However, we did not do any laboratory tests to detect it.

We, of course, are aware of the skin lesion of phenylketonuria, so much so that we have done amino acid analyses on the plasma of eczema cases. There was no alteration in amino acid patterns in the cases of eczema we have studied thus far.

16. The Systolic Blood Pressure in Neonatal Asphyxia and the Respiratory Distress Syndrome. GERALD NELIGAN, D.M.* Department of Pediatrics, Harvard Medical School, Boston. Introduced by Clement A. Smith.

Systolic pressures measured by a sphygmomanometer with a one-inch cuff, and a sensitive xylol-filled pulse indicator, have been compared with simultaneous direct measurements from a catheter in the aorta in six newborn infants. In three of them results by the two methods were identical; in three, the results with the sphygmomanometer were about 10 mm. Hg higher. The lowest pressure recorded for each infant was reached within 24 hours (usually 4) after delivery.

This sphygmomanometer has been used to follow changes in systolic blood pressure from a few minutes after delivery in 84 infants classified as shown in the Table.

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Changes in Systolic Blood Pressure in Newborn Infants

Clinical Category and No. of Infants	Initial Pressure, Mean	Lowest Pressure	
		Mean	Range
37 mature normal, delivered vaginally	84	56	44-76
13 mature asphyxiated	98	58	50-72
14 elective Cesarean section	76	58	48-70
10 well infants of diabetic mothers	67.5	60	50-70
2 distressed infants of diabetic mothers (1 died of hyaline-membrane disease)		38	38
5 well premature	65	49	44-52
3 distressed premature (2 died of hyaline-membrane disease)		37	32-42

That the relatively high initial systolic pressures of normal mature babies may be at least partly due to chemical asphyxia during vaginal delivery is suggested by the even higher initial pressures found in the 13 infants who underwent postnatal asphyxia, in that they took longer than two minutes to establish regular respirations. Moreover, lower initial pressures were found in the 14 infants delivered by elective cesarean section.

Of the 12 infants of diabetic mothers, eight were delivered by elective section. Both of those who developed severe respiratory distress showed a transient fall of systolic pressure to 38 mm. Hg within the first half-hour. One of the ten who maintained normal pressures showed some respiratory distress, but this lasted less than two hours.

Of the eight premature infants, all three who developed significant respiratory distress also showed a transient fall in pressure to below the normal range in the first half-hour.

The findings reported indicate that the newborn infant has a well-developed vasopressor response to chemical asphyxia. They also suggest a significant connection between transient hypotension during the first half-hour of life and the development of the hyaline membrane syndrome.

Discussion

DR. SYDNEY SEGAL, Vancouver, B. C.: On the basis of this eloquent presentation and a study by Martinek, Hardy, and me in progress since 1956, I would suggest that Dr. Neligan's method and ours both suffer from one disadvantage: To detect an end-point, the infant must be quite placid. If Dr. Neligan's infants have been as prone to thrash their limbs about as ours did for their first 15 minutes, I think there is added reason for complimenting him on the diligence with which he has been able to collect so many data.

We have noticed that an infant who is asleep may have a systolic blood pressure which is some 10 to 15 mm. of mercury lower than when he awakens, though he remains quiet and passive enough for us to obtain repeatedly a good end-point. Ours is a recording method, so perhaps we can tolerate a little more disturbance in the infant.

I wonder if Dr. Neligan would like to comment on the fact that our own data on normal infants do not show this great propensity that we see on his slides, to drop from an initially high systolic level at birth.

Our main interest has been in babies who either have the respiratory distress syndrome or who are candidates for this form of disturbance. Our results on these are quite similar to Dr. Neligan's, which is most reassuring to us.

DR. GERALD NELIGAN: It's nice to have Dr. Segal's support on the question of hyaline-membrane disease. As I said, I don't think we fully understand all the snags of the indirect method. The only major advantage is that it is so innocuous that frequent readings can be taken at short intervals over long periods of time.

The effect of movement, of course, precludes operations until the baby is reasonably quiet, but we have felt it possible to take some rather more snap readings, I think, than Dr. Segal would accept. We're also interested in what Dr. James may be able to tell us not only about chemistry but about blood pressures recorded by the direct method in the first hour or two of life. Of course, I feel that the snags which Dr. Segal has mentioned may be, in fact, leading us to draw false conclusions.

DR. L. STANLEY JAMES, New York: We were interested to see Dr. Neligan's results showing that the blood pressure of many newborn infants was higher at birth than at one hour of age. Our studies have led us to conclude that during the delivery process the majority of infants are exposed to a brief period of biochemical asphyxiation. Experimentally, such mild or brief asphyxiation is associated with a rise in blood pressure. However, a prolonged period when the pH may fall below 6.9 leads to cardiovascular collapse and a fall in blood pressure. The raised pressures in the normal infants and the lower pressures in the distressed might well be explained in terms of the degree of asphyxiation.

Direct intra-arterial pressure measurements of blood pressure using a catheter in the umbilical artery have indicated that vigorous normal infants who breathe within seconds of delivery show little fall in pressure over the first hour. I would be interested in knowing how often Dr. Neligan observed this in his series.

DR. PAUL R. LURIE, Indianapolis: I think your slide which showed the situation with asphyxia during surgery is very interesting in that it shows, with one exception, a rather perfect reciprocal relationship between pulse and systolic blood pressure. I wonder if Dr. Neligan wishes to say which is the chicken and which is the egg in this situation? It does serve to remind us that blood pressure is the result of a large complex of factors

that are changing all the time and that peripheral resistance or vasomotor tone is not equivalent to blood pressure. I'm sure the authors are well aware of this, but that slide illustrates beautifully what might happen if vasomotor tone and cardiac output remained constant, yielding this reciprocal relationship between pulse and blood pressure by variations of stroke volume.

DR. NELIGAN: I'm not an authority on this, but have read some interesting observations by Berthoud and Zlotnik (*Cardiologia* 20:58, 1952) concerning a man who had complete respiratory paralysis due to poliomyelitis and who insisted on being taken out of the iron lung to see how he got on. He always got on very badly and soon lost consciousness. His doctors took the opportunity to follow his biochemical and cardiovascular changes and they found that if they ventilated him with oxygen just well enough to keep his oxygen saturation from falling too low, they could eliminate the bradycardia, but if they wanted to eliminate the hypertension as well, they had to keep his CO_2 accumulation down. They therefore concluded that in this patient the rise in blood pressure was due to CO_2 accumulation and the bradycardia to oxygen deficiency. In the patient illustrated by my slide there was a second episode where the anesthetist got into some difficulties, but at this stage the baby was being ventilated with pure oxygen and developed a hypertension of the same degree as previously, but no bradycardia.

DR. CHARLES D. COOK, Boston: Dr. Neligan avoided speculation on the relationship between the mechanism for hypotension that he has observed in the infant with respiratory distress and the pathogenesis of the hyaline-membrane syndrome. Epinephrine has been used in these infants with reported beneficial effects but, at least in experimental animals, epinephrine shifts blood from the peripheral vessels into the pulmonary vascular system. Thus I wonder whether one should treat the hypotension or avoid pulmonary congestion? I wonder if Dr. Neligan would comment on these points.

DR. NELIGAN: On the first point of mechanism, I'm not employed as an advertising agent, but I think that it should be left to those interested to come back on Saturday morning and hear a discussion of this subject further by some of my colleagues from Boston, Dr. Rudolph and Dr. Drorbaugh.

On the question of the use of pressor agents, I am afraid that I know no more than Dr. Cook.

DR. ROBERT H. USHER, Montreal, Canada: I would like to comment on and ask about several aspects of Dr. Neligan's very fine paper. Some of these findings I can amplify from my own experience gained from taking some 500 flush blood pressure determinations on 100 permature infants, approximately half of whom were showing signs of the respiratory distress syndrome. The results obtained showed a similar pattern to that which he has observed. The distressed infants had lower pressures during the first six hours of life, so that in the smallest weight group the mean pressure for distressed infants was 25 mm. Hg and for nondistressed infants 50 mm. Hg. In both groups the pressures rose during the ensuing four days with the gap between the two diminishing, though persisting, until one week of age. The somewhat lower results obtained by my flush method may be due to the fact that the flush represents the mean blood pressure whereas the two-cuff method registers systolic pressure.

The premature infants I have studied have never shown the drop in blood pressure during the first minutes of life, their pressures being lowest during the first 10 minutes and rising thereafter. I would like to join Dr. James in asking Dr. Neligan whether this average drop which he describes is characteristic of all infants during the first minutes of life, or whether the averages portrayed on his graph may be exaggerated by severe drops in a few cases? If this is a universal finding with the two-cuff and not with the flush method, it may well represent a widened pulse pressure at birth narrowing during the first minutes of life, rather than a falling blood pressure; such a widening of the pulse pressure would not be picked up with use of a flush method.

I would certainly congratulate Dr. Neligan on his clinical observations. There has been too little detailed clinical observation of the respiratory distress syndrome in spite of the fact that the diagnosis always rests on clinical grounds.

An associated observation which I have made during the past two years is that hypotension secondary to fetal hemorrhage at delivery in one full-term and two premature infants was associated with the classical signs of the respiratory distress syndrome. The response to blood transfusion in these infants was most interesting; within two hours the retraction, grunting, and decreased air entry on auscultation had disappeared along with relief of the hypotension.

These experiences with fetal hemorrhage are of interest in that they lead one to suspect that hypotension may be primary in respiratory distress syndrome and not simply a result of the distress. Certainly I would agree with the many observers who have noted that the retraction and grunting begin right at birth in affected cases, and at this time the only associated clinical finding that I have observed is hypotension, the remainder of the clinical signs taking 12-24 hours to develop.

Concerning the need for a quiescent state and the effects of stimulation when making a blood pressure determination, I have noticed that the prema-

ture infant during the first several days after birth shows only minimal hypertensive response to handling, while a one-week- to two-month-old infant may double his flush pressure with stimulation. One last point that should be mentioned is that there is a direct correlation between blood pressure and birth weight during the first days of life and that any comparison of blood pressure in distressed premature infants should be made with nondistressed infants of the same weight.

DR. NELIGAN: Thank you, Dr. Usher. The only point I think I should comment on is this question of other people not always finding an initial fall in blood pressure. I agree that the fall varies greatly, and, particularly in prematures, there may be none. In mature babies I think I've always found a fall. This is a point about which I don't feel on very strong ground.

DR. RALPH PLATOU, New Orleans: I hesitated to rise, knowing discussion of this nice work would be heavy. A rather ingenious idea of measuring the systolic point through visualization of an air bubble in a column of xylol incorporated in the apparatus, was conceived by one of our medical students—now Dr. John Fordtran. It's a real pleasure to see the modification and fine application of the apparatus reported now by Dr. Neligan. We also have modified the method slightly, we think toward even further simplification.

As our experience grows, we see more and more variations in early blood pressures, particularly among the prematurely born infants. When these are matched with simultaneously recorded venous pressures, pulse rates, respiratory rates, and other indices, we see all degrees of overlapping in values, individually or collectively, related to subsequent fate of the infants. We have gained the conviction that so far, not a single measurement of any sort has had clear-cut and definitive predictable prognostic significance.

17. The Response of the Newborn Baby to Inflation of the Lungs. K. W. CROSS, M.D.*; MARSHALL H. KLAUS, M.D.*; WILLIAM H. TOOLEY, M.D.,* and KURT WEISSER, M.D.* From the Cardiovascular Research Institute and the Department of Pediatrics, University of California Medical Center, San Francisco. Introduced by Edward B. Shaw.

The lungs of newborn infants have been inflated by positive pressure applied through a face mask while the baby slept in a body plethysmograph. There have been two findings of considerable interest:

1. With a satisfactory inflation there is generally a Hering-Breuer reflex, i. e., there is a period of apnea with the inspiratory muscles relaxed.

2. In a proportion of the infants we have elicited Head's paradoxical reflex, i. e., there is a primary rapid inspiratory gasp followed by the apneic response just described.

These findings are thought to have both theoretical and practical implications.

Discussion

DR. LOUIS GLUCK, New York: Could you assure yourself that you were inflating the lungs and not the stomach as well? Anyone who has done this in the newborn knows how difficult it is to inflate the lungs and not the stomach. Perhaps your reflex might have been related to distension of the stomach as well as of the chest.

DR. KURT WEISSER: Our method allows us to record continuously changes in volume of the infant's body. After release of the positive pressure, the babies always exhaled instantaneously and came back to the volume which had existed before the inflation was done. Any air delivered to the stomach would have had to have been exhaled together with air from the lungs immediately after the release of positive pressure. This is very unlikely.

DR. L. STANLEY JAMES, New York: We are indebted to Dr. Weisser for the demonstration of these reflexes in the newborn, and everybody interested in respiratory physiology will be intrigued at the possibility of having a way of measuring cardiac output and pulmonary blood flow in newborn babies.

We have noted the response to positive pressure when resuscitating nonbreathing infants. During the first or second application of positive pressure to the endotracheal tube, the limp and depressed infant will frequently inspire, augmenting the resuscitation. The presence of these rapidly adapting stretch receptors in the tracheobronchial tree may explain why some of the apparatus used for resuscitation, capable of delivering pressures which will not expand alveoli, are yet apparently effective.

Pressures of at least 16 cm. of H_2O appear to be necessary to evoke Head's paradoxical reflex. In consequence, if the swallowing movements recently described by Bosma and Glynn are effective in stimulating this reflex, pressures of this

* By invitation.

range must be reached. This interesting mechanism might be tested by inserting a pharyngeal airway before the first breath occurred.

DR. WEISSER: I may, perhaps, comment that Head's paradoxical reflex is a rather undifferentiated reflex phenomenon, which can be elicited even in an organism damaged by anoxia. One evidence for this is, that if the afferent vagus fiber is cooled, the reflex is abolished only at the low critical temperature of 6-4 C. In comparison, the Hering-Breuer reflex disappears at a cooling temperature as high as 12-10 C.

DR. SYDNEY SEGAL, Vancouver, B. C.: We are aware of the relatively high pressures required for initial inflation of the lungs of apneic newborn infants. We have also been concerned about the much lower limits of pressure available in mechanical resuscitating machines which, at one time, had to be approved by a Council of the American Medical Association. And yet, experience has shown that when such a lower pressure apparatus has been applied to the mouth of an apneic baby it has often been successful in that inflation of the lungs has taken place, the infant's first gasp following immediately after the mask application. It is likely, as I have heard Dr. James suggest occasionally, that the low pressure exerted by such an appliance on some part of the infant's airway is effective when it can evoke a reflex response in the form of a forceful inspiratory gasp, a gasp which develops across the lung the great pressure gradient required for initial inflation.

The actual demonstration of Head's paradoxical reflex, as we have just heard it described, must be the response through which these low-pressure machines may be effective.

18. The Electrocardiogram in Children with Ventricular Septal Defect and Severe Pulmonary Hypertension: Correlation with Response of Pulmonary Arterial Pressure to Surgical Repair.

JAMES W. DUSHANE, M.D.*; WILLIAM H. WEIDMAN, M.D.,* and ROBERT O. BRANDENBURG, M.D.* Section of Pediatrics and Section of Medicine, Mayo Clinic, Rochester, Minn. Introduced by Haddow M. Keith.

In patients with ventricular septal defect having a left-to-right shunt the pulmonary blood flow is greater than the systemic, and this extra volume of blood returns to the left side of the heart, resulting in an increase in the work of the left ventricle. With a balanced or a dominant right-to-left shunt there is no increase in pulmonary blood flow and no increase in the work of the left ventricle.

The electrocardiogram, when properly interpreted, reflects the increased work by the left ventricle. Thus, electrocardiographic evidence of increased left ventricular output in patients with isolated ventricular septal defects should indicate an elevated pulmonary blood flow, regardless of the level of pulmonary arterial pressure. Closure of a ventricular septal defect results in a fall in pulmonary arterial pressure if the pulmonary blood flow is increased, but no change in pulmonary arterial pressure if pulmonary flow is not increased.

We independently reviewed 100 electrocardiograms of children with ventricular septal defects having pulmonary arterial pressures of 80% to 100% of systemic. Electrocardiograms of children with no demonstrable heart disease were intermixed as controls. Using electrocardiographic criteria of the Mexican school as modified by DuShane, each of us predicted the presence or absence of increased work by the left ventricle.

Results of these predictions were compared with the changes in pulmonary arterial and systemic pressures measured before and after repair of the ventricular septal defect at the time of operation. Comparison of the fall of pulmonary arterial pressures, indicating a preexisting left-to-right shunt, with electrocardiographic evidence of increased left ventricular work, revealed a correlation of 96%, indicating a high degree of reliability in assessing pulmonary blood flow from the electrocardiogram.

Criteria for the selection of patients for surgical treatment in this group with severe pulmonary hypertension have been controversial. Our earlier experiences impressed us with the reliability of the electrocardiogram in determining increased pulmonary blood flow despite severe pulmonary hypertension. This study was undertaken to test the validity of this concept.

* By invitation.

Discussion

DR. JOHN D. KEITH, Toronto, Canada: This slide shows the percentage of cases with a Q wave in V_6 over and under 1 mm. in size, in tetralogy of Fallot and ventricular septal defect. In tetralogy of Fallot 74% had a Q wave of less than 1 mm. and 26% over 1 mm., while in ventricular septal defect, 20% were less than 1 mm. and 80% over 1 mm.

In the 26% of tetrads with a Q wave in V_6 over 1 mm., all but one had a good blood flow to the lungs, as one finds in atypical tetralogy of Fallot or after a successful Blalock operation.

In the cases of ventricular septal defect, with large Q waves in V_6, one also finds a generous pulmonary flow.

As a general rule, tetralogy of Fallot represents a low pulmonary flow with high resistance, and such cases are associated with a small or absent Q wave in V_6. In the cases of ventricular septal defect who develop an electrocardiographic pattern similar to that of tetralogy of Fallot, with a small Q wave in V_6, 1 mm. or less, one finds the hemodynamics of high resistance and low pulmonary flow. Such cases are not suitable for surgical correction.

Dr. Weidman has set down good criteria for those who are sure to do well at operation, but he does not help us with the borderline cases. One of his criteria is a Q in V_6 of 4 mm. We believe, a Q in V_6 of 1 to 4 mm. may frequently indicate the possibility of successful surgery, especially one that is associated with a pulmonary flow of over 150% of systemic.

DR. ALEXANDER NADAS, Boston: I would like to agree in most regards with what the Mayo group has presented. It's very important to emphasize the usefulness of the electrocardiogram in the evaluation of the functional status of ventricular defect. At the same time, I think it is also important to emphasize the use of other available tools in evaluation of ventricular defects. I think whenever you put up one tool to be the all-deciding thing it's wrong. These people use other criteria: good physical examination, x-rays, the hyperactivity of the heart, the lung fields, all of which are very important criteria in deciding operability or inoperability. Obviously, all these things are extremely important tools, and I don't think any one of them ought to be regarded as the only tool or as the most decisive one. I think a composite judgment is best.

I would like to see these ECG's correlated with physiologic data of resistances and flows. These would make Dr. Weidman's figures a little more meaningful than simply taking a drop in pressure after operation as the criterion of correlation.

DR. HOWARD JOOS, Los Angeles: I'd like to ask whether any of your patients with these criteria had an endocardial cushion defect.

DR. WILLIAM H. WEIDMAN: None of the patients who were presented here today had an endocardial cushion defect. I suppose that the reason you ask is that several of these patients had a counterclockwise loop with the QRS vectors in the frontal plane. The type of counterclockwise loop seen in patients with ventricular septal defect is often not that type which has been described previously as associated with an endocardial cushion defect. In the two electrocardiograms demonstrated today, the initial counterclockwise loop was below the horizontal line; usually in endocardial cushion defect the initial loop is either on the horizontal, or above the horizontal line.

Dr. Nadas, I can give you no data today on the correlation of these electrocardiograms with the physiologic data that we have. Not all of the patients, as you know, had cardiac catheterization. Some had studies of response of pulmonary artery pressure to oxygen and/or acetylcholine; we have looked over this data in a preliminary way, but haven't been ready yet to make any formal comparison.

DR. HELEN TAUSSIG, Baltimore: I just want to say that I am sure you have correlated your electrocardiographic findings with the other findings in your patients, and I agree with Dr. Nadas that one must take the entire picture into consideration. The importance of your observations is that they give us a simple tool, available to us all, and, after all, our constant striving should be for the simplest method which will give us a high degree of accuracy. You should be congratulated on your demonstration of the value of a simple tool which will help greatly in the evaluation of these cases.

DR. WEIDMAN: We do use all factors we can find in evaluating each and every patient. I would like to emphasize that the absence of evidence of left ventricular overwork in the electrocardiogram, using those criteria presented today, does not necessarily mean that the pulmonary flow is not increased. There may be certain nebulous criteria which at present are not definable; consequently, the physical examination, an x-ray of the chest, and even cardiac catheterization is used to evaluate these most difficult cases.

19. Evaluation of the Pulmonary Vascular Bed in Infants and Children. FORREST H. ADAMS, M.D.; I. HUNTER CRITTENDEN, M.D.,* and HARRISON LATTA, M.D.* From the Departments of

* By invitation.

Pediatrics and Pathology, University of California Medical Center at Los Angeles.

Vascular changes associated with pulmonary hypertension in patients with left-to-right cardiac shunts have been shown to be an important factor in operability. Pulmonary resistance to flow is effected by vascular alterations, prominent among which are medial hypertrophy of small muscular arteries and subsequent intimal proliferation. Vessels showing medial hypertrophy are considered capable of vasodilation and constriction; hence increased pulmonary resistance associated with medial hypertrophy is theoretically reversible. On the other hand, intimal changes, when extensive, can produce marked resistance to flow and may fix the vascular bed in a state incapable of dilatation.

Thirty-four patients with pulmonary hypertension were studied with use of acetylcholine injected into the pulmonary artery to determine the distensibility of the pulmonary vascular bed as an index of severity of vascular disease. Thirty-one of the above had left-to-right intracardiac shunts and the other three did not. The patients' ages ranged from 2 months to 14 years. Eleven of the patients failed to respond to the drug. All of these were over 6 years of age, and the left-to-right shunt was small (less than 100% of the systemic flow). Twenty-three of the patients responded to the drug by a drop in 10-20 seconds of the pulmonary artery pressure by 10%-31%. The left-to-right shunt in these patients was at least 140% of the systemic flow. In eight of the patients, sections of the lung were available for microscopic study. Severe intimal proliferation was associated with a lack of response to acetylcholine. Muscular hypertrophy and mild intimal proliferation did not appear to interfere.

This study suggests that the severity of vascular disease in pulmonary arteries in patients with pulmonary hypertension due to left-to-right shunts may be evaluated preoperatively by measuring the changes in pulmonary pressure and flow following an injection of acetylcholine.

Discussion

DR. HELEN TAUSSIG, Baltimore: I would like to challenge the statement that patients with small ventricular septal defects will develop pulmonary hypertension by 15 years of age or, at least, by very early adult life. Small ventricular septal defects are compatible with long and active life and do not lead to pulmonary hypertension. Have you any evidence that they ever develop pulmonary hypertension? I even challenge the statement about patients with auricular septal defects developing pulmonary hypertension; many of them do not. I think that we have become unnecessarily afraid of the development of pulmonary hypertension and that we should get a very clear concept in our minds as to when it does and as to when it does not develop.

DR. FORREST H. ADAMS: As I understand the question, Dr. Taussig does not disagree with the findings just presented but rather questions certain interpretations contained in the slide on *the evolution of pulmonary hypertension.* In this slide we attempted to show the course taken by patients with large ventricular defects as compared with patients with small ventricular or atrial defects. This latter group do not develop pulmonary changes, if at all, until late adolescence or early adulthood.

DR. TAUSSIG: Yes, but there is a great deal of evidence offered to try to urge people to close small ventricular septal defects early, and I think it is a very, very dangerous thing to do so. I think it should be made clear before this Society that patients with small ventricular septal defects do well and that we should have no fear of their developing pulmonary hypertension.

DR. ABRAHAM M. RUDOLPH, Boston: We have observed similar findings in patients being catheterized.

One thing that I'd like to stress which perhaps Dr. Adams didn't stress adequately was the measurement of systemic arterial pressure at the same time as pulmonary arterial pressure. When acetylcholine is infused into the venous system there is a general hemodynamic response to the substance. In patients with large ventricular septal defects with equalization of pressure in the right and left ventricles even a very small amount of acetylcholine which passes into the systemic circulation through a small right-to-left shunt or across the lung capillaries, may produce enough drop of systemic arterial pressure to produce an apparent response in the pulmonary vasculature, which is merely due to the drop in systemic

arterial pressure with a simultaneous lowering of right ventricular and pulmonary arterial pressure.

Several instances have been observed with no response in pulmonary arterial pressure and pulmonary vascular resistance, and with increase in the right-to-left shunt at the ventricular level due to a decrease in systemic pressure.

One other point is that, although these findings are of interest and do suggest very definitely that these are functional elements in pulmonary hypertension of congenital heart disease, I do feel that we should not regard this as the only important factor in making decisions regarding surgery. We have observed one situation, and possibly another, in which there was no response to acetylcholine in a patient with severe pulmonary hypertension but who did have a left-to-right shunt and who came through surgery without any problem. So I do not feel that this should be the final deciding factor.

DR. ADAMS: I agree with both points.

DR. WILLIAM H. WEIDMAN, Rochester, Minn.: I would like to ask Dr. Adams if acetylcholine studies have been done on the same patient at intervals to demonstrate the presence or absence of change of pulmonary artery response to acetylcholine. It would be very interesting to know if the patient had responded at one time, and then failed to respond at a later date; this may give us a lead in thinking about the "life history" of the ventricular septal defect. Secondly, I would like to add to Dr. Rudolph's comment, that we have had at least one patient who demonstrated a significant fall of pulmonary artery pressure following acetylcholine, but in whom the pulmonary artery pressure failed to fall significantly at the time of surgical closure of the ventricular septal defect.

DR. ADAMS: We have not made any longitudinal studies in patients.

DR. ALEXANDER NADAS, Boston: We have been quite interested in this same topic as Dr. Rudolph mentioned a minute ago. We are expressing resistances on a square meter basis rather than on the basis of the actual flow of the patient. This changes the very high resistances of young infants with very slow flows to figures more nearly compatible with those of the adult. We don't know whether this is good or not. This is what we have been trying to do the past year or two.

I would like to ask Dr. Adams whether the calculated resistance to acetylcholine response gives him more information than the absolute level of resistance. In other words, can you separate out with acetylcholine a patient with a resistance of say 12 or 15 units, some of whom will respond to acetylcholine whereas others won't. Is this more than the actual expression of the height of the resistance and can this be used more reliably in terms of prognosis as to what will happen to the resistance chart?

The final point I'd like to make is that I'd like to join Dr. Taussig's remarks in the matter of prognosis and indeed to go a little bit farther in that even in the medium-sized child whom we study some years after the initial study, we are unable to find any significant change in the absolute level of resistance. Now, perhaps these patients at the first study would have responded to acetylcholine whereas in the second study they would not, but the absolute level of resistance through a matter of years and certainly beyond six years of age has not changed.

DR. ADAMS: Dr. Nadas has raised several points: 1. In Boston they like to express pulmonary resistance in relation to surface area. We do not find this a valid concept. Resistance should be expressed only in absolute terms, i. e., units or dynes.

2. What is the relation of the absolute resistance to the presence or absence of response to acetylcholine? We have not calculated our data as yet in this fashion. It is a good suggestion.

20. Clinical Observations on Twenty Hydrocephalic Children Subjected to Ventriculoatrial Shunt: A Preliminary Report. DAVID B. SHURTLEFF, M.D.,* and ELDON L. FOLTZ, M.D.* Departments of Pediatrics and Neurosurgery University of Washington School of Medicine, Seattle, Wash. Introduced by Robert A. Aldrich.

Twenty hydrocephalic children were studied before and after a CSF shunt was established between the lateral ventricle and the right atrium of the heart, using a Heyer valve. The cause of the hydrocephalus was accurately established by thorough neurosurgical work-up in all instances prior to the shunt procedure. Likewise, all cases were shown to have advancing hydrocephalus as proved either by persistently elevated intraventricular pressures (over 120 mm. CSF) under basal conditions, by progressing ventricular enlargement as shown by serial ventriculograms, or by steadily enlarging head as shown by daily head measurements. The diagnosis of communicating hydrocephalus was established in 18 of the children, and in 2 the hydrocephalus was the result of congenital cyst of the

* By invitation.

foramen of Magendie (Walker-Dandy syndrome).

The head circumference was measured repeatedly throughout the course of these studies and plotted against the accepted normal graphs for this parameter. Using a standard x-ray technique for limited air ventriculography, the frontal cortex width was measured in centimeters prior to operation and at intervals thereafter. The majority of these studies were done on the ward.

After establishing the valve shunt, every case showed a prompt fall of ventricular pressure to normal levels, and head enlargement ceased abruptly. Subsequent air "bubble" studies (limited ventriculograms) demonstrated a significant increase in the measurable frontal cortex thickness, at times an increase of 1.5 cm. in two months. The status of the anterior fontanelle was found to be unreliable as an index of the advance or regression of the hydrocephalus except for very gross changes. In the course of these studies, the valve became obstructed on a few occasions, and in these instances the above sequence was abruptly reversed. Revision of the shunt resulted in prompt improvement.

Six infants in the group had lumbar myelomeningoceles which were bulging and oozing CSF. Serious threat of meningitis was present. External evidence of gross hydrocephalus was lacking, but the ventricular pressure and air studies showed that significant ventricular enlargement without ventricular obstruction was already present. The shunt procedure was therefore done urgently. Prompt collapse of the myelomeningocele occurred, with rapid epithelialization of the weeping surface of the sac. Meningitis was avoided with relatively little stress to the child as compared with the stress involved in a direct attempt to close a large, weeping myelomeningocele. The complications of the latter procedure, i. e., rapid hydrocephalus and additional lower extremity neurological damage, were avoided by treatment of the hydrocephalus first. Only two of these patients were subsequently operated on to achieve plastic repair of the myelomeningocele. The other four healed in well without direct operation.

This program of adequate diagnosis, early treatment, and long-term follow-up of children with progressing hydrocephalus is not completed, but has already heavily emphasized that if ventricular pressures can be maintained at 120 mm. of CSF or below, frontal cortex width or depth will increase considerably—even dramatically at times. Thus, progressive brain damage may be averted. The program outlined is a relatively simple one which can be attained without great difficulty, provided constant attention to detail is maintained. These initial results appear well worth such an effort.

Discussion

DR. CHARLES KENNEDY, Philadelphia: Other groups who have used this type of valve have encountered a variety of complications. One of these is infection, which is often difficult, if not impossible, to eradicate. This is apparently because bacteria become lodged in the valve itself. Seeding from this source results in recurrent sepsis. Another complication is blockage of the tube with tissue fragments. With what frequency did you encounter these or other difficulties in the group of patients presented?

DR. DAVID B. SHURTLEFF: Of the 20 patients, 8 have had a total of 20 obstructive episodes of which 18 necessitated surgical revision. A blood clot following an acute bleeding episode obstructed valves twice. Four other patients, including two who account for 14 occlusions between them, had fibrin clots in or about one end of the shunt tube. I would like to emphasize that, except for the two children with acute bleeding episodes, all the children with obstructive episodes had inflammatory cerebrospinal fluid findings prior to surgery. I should add that the only child with an obstructed shunt at the time of death had a massive mural thrombus involving the superior vena cava and right heart.

We recognize only two children with infection as evidenced by culture or pathologic tissue examination. One child developed wound sepsis four days after a revision of the shunt and subsequently died with staphylococcal ventriculitis and pneumonia. The second child developed staphylococcal ventriculitis prior to placement of her shunt. Although we believed her infection cured, she

developed a very stormy postoperative course and died two weeks later. Repeated cerebrospinal and ventricular fluid cultures showed no growth postoperatively, but pathologic examination revealed many organisms in the tissue surrounding the brain and in brain tissue itself. I have mentioned that five of our eight patients manifested fever as part of their response to obstruction of the valve. In each case release of the obstruction produced prompt remission of clinical signs.

DR. LEO J. GEPPERT, Fort Sam Houston, Texas: I think most of us in pediatrics are weary of having our beds full of hearts and heads. This operation has a great administrative advantage because the tube can be put in place and the patient discharged within a week.

I would like to know if you have any tricks for unplugging this tube and how many revisions you think are justified?

DR. SHURTLEFF: First, in regard to your statement, "in a week they're out," I think that perhaps, before you evaluate any results, you ought to review of the work of Dr. Laurence in the *Lancet*, which shows about 45% of all congenital hydrocephalics had spontaneous remission. I found while reviewing many papers that the authors report, in most cases, less than 45% of operative cases as successful. This may indicate surgery may do more harm than good. Secondly, our data to date would strongly suggest that careful work-up prior to surgery in order to establish the cause of the symptom, hydrocephalus, and to detect the presence of progressive disease or inflammatory processes, is essential to proper evaluation.

We have had no difficulty in unplugging the tube.

The only way I can answer your second question is to ask how many times do you treat a child with chronic otitis media? I think that, once you have selected a suitable candidate for the initial operation, you should revise the shunt until the child dies, has a successful decompression, or develops a spontaneous arrest.

DR. HENRY BAIRD, Malvern, Pa.: I would like to ask how much faith you have in measuring the cerebral mantle as a guide to the value of the shunt and as an indicator of the degree of future intellectual development?

DR. SHURTLEFF: All we can say at present is that by following serial measurements of cerebral mantle thickness we can obtain some concept of the effects of various intraventricular pressures. Our data seem to indicate that a normal pressure would allow normal growth of brain tissue as well as expansion of brain tissue previously subjected to abnormally high intraventricular pressure. An abnormal pressure thins out the cerebral mantle or holds an already thinned mantle in a state of compression. Frontal cortex width as well as intraventricular pressure may, at times, have no relation to the functional state of the valve since some children will have spontaneous arrest with their valve in place and obstructed.

The second portion of your question is extremely important. We arbitrarily selected 1 cm. of cerebral mantle as a minimum requisite for inclusion in our study. However, Dr. Laurence in his paper reports two children with 0.5 cm. of frontal cortex and with intelligence quotients of 85 and 100. I don't think the anatomic evaluation of how much brain is present would necessarily have any prognostic value for estimating future potentialities in the light of our present knowledge. On the other hand, I think that to preserve normal architecture should be of some help, as there is evidence that elevated intraventricular pressure produces psuedoporencephalic herniations, squeezes tissue fluid out of the brain and prevents the development of myelin. At present, more data are needed on the relationship of intraventricular pressures, cerebral mantle thicknesses, autopsy tissue changes, and long-term evaluation of patients' development.

DR. ROBERT B. LAWSON, Miami, Fla.: You just touched on something that I think is very important, namely, spontaneous arrest of hydrocephalus. We have been interested in spontaneous arrest of the hydrocephalus in these children where there is no specific cause.

How long do you wait and how do you evaluate them before you operate so that you will not be operating on those that are going to spontaneously arrest? After you have operated on these children, how many of them have eventually been able to do without the shunt?

DR. SHURTLEFF: We cannot, as yet, answer your question as to how many of our patients are able to do without their shunt. We had originally planned to investigate the need for the shunt yearly, but an interruption has developed and, as a result it will be two more years before we can answer your question. We plan to obstruct the tube where it passes subcutaneously and observe the children for evidence of intraventricular hypertension. We have had four patients with sudden increase in intraventricular pressure over one year after decompression. Because of the suddenness of onset of symptoms, which were promptly relieved by revision of the shunt, we feel the intervening period of normalcy was dependent on the functioning of the valves.

Since we have noted as much as 1 cm. decrease in frontal cerebral mantle in one week, preoperative observation has been purposely short. A quick review of all types of shunt procedures reveals that many will function properly for short periods of time. Furthermore, any hospital for the mentally retarded contains evidence of the sig-

nificant morbidity associated with arrested hydrocephalus. One extremely important use of the existing procedures should be to relieve intraventricular hypertension until natural processes of formation and absorption of cerebrospinal fluid develop. Such patients should be carefully studied to determine when the shunt is no longer needed. They should also be followed to evaluate the effect of decompression, if any, on the morbidity.

DR. W. N. GIBSON, Cleveland: In quoting K. M. Laurence's (*Lancet*, 1958, p. 1152) 40% figure for the spontaneous arrest rate in hydrocephalus we have to keep in mind the natural selection operative in his material. Many of the patients dealt with in your series would have died in the first few months of age without treatment. The cases reviewed by Laurence were taken from a clinic where they were referred. They were not representative of the worst cases, which may die in the first three to six months.

DR. SHURTLEFF: That is correct. We attempted to study patients as early as possible. We investigated approximately 70 patients. Many of the younger patients were not accepted because of severe brain damage incurred in utero. We also observed a number of cases which were, by our criteria, no longer progressive disease. Two of the latter group returned with abnormal head growth, recurrence of high pressure, and decrease in mantle thickness, evidence of intermittently progressive hydrocephalus.

DR. W. A. NEWTON, Columbus, Ohio: Since the tenor of the discussion concerning this paper has been favorable, I think that two comments should be made. In a large series of ventriculoatrial shunts (over 120), we have had very encouraging results similar to those presented by Dr. Shurtleff. In addition, however, I would like to make the following comments concerning two apparently inevitable sources of complication.

The formation of a mesothelial investment around the thoracic catheter of the shunt is felt to be a foreign-body reaction and probably starts with reaction and clot at the point of entrance into the jugular vein. The reaction then promulgates distally along the catheter, and in the very young rapidly growing children may eventually cap the thoracic end of the shunt as it pulls up with the child's growth. This "vegetation" has served as a nidus for clot formation, and as a site for implantation of bacteria, as in rheumatic valvulitis, in 8% of our large group of patients. This has been combatted by (1) reducing the bulk and lumen of the thoracic catheter, (2) maintaining maximum blood flow at the point of entrance into the jugular vein with use of a five purse-string suture with no permanent venous obstruction, and by installing the thoracic end of the shunt at the tricuspid valve to delay need for growth revision as long as possible.

The second comment is simply an observation that we confirmed for our neurosurgeon concerning the nature of the material which may be found obstructing the lumen of the ventricular end of the catheter. In addition to fibrin described by Dr. Shurtleff, more frequently we find that the lumen is plugged by the choroid plexus in a peculiar sort of way. The choroid plexus seems to have a tendency to swing into the lumen of the tip of the catheter plugging it, similarly to the movement of the omentum in the peritoneal cavity. I'm sure those who are working with this surgical procedure will encounter these types of complications.

DR. SHURTLEFF: Thank you. We have not recognized any of these complications. One of our patients died at home, however, and postmortem examination revealed no significant cause. We place the distal tip of the tube by fluoroscopy in the area of the atrium in an attempt to allow as great a blood flow as possible to swirl by the opening which oozes cerebrospinal fluid. This attempt to dilute the cerebrospinal fluid quickly is based on previous clinical experience with shunts into the venous tree that quickly clot, and on the in vitro studies of Dr. Bovi of Italy, who observed that small amounts of inflammatory spinal fluid accelerate the blood-clotting mechanism.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: Dr. Shurtleff, if you will accept another question, I should like to ask if you have made observations concerning the transport of such substances as urea and glucose across the blood-brain barrier in cases of hydrocephalus?

Dr. Williams, of our department, has obtained rather inconsistent results in his studies of babies with hydrocephalus, and in a few observations on dogs; but has found in certain cases evidence that transport of these materials may be abnormal in the babies with hydrocephalus.

DR. SHURTLEFF: We instituted several types of dye studies and became discouraged. The studies by Adams, Bering, Sweet, Laurence, Selverstone, and others using various dyes, radioactive tracers, and heavy water, indicate that these substances are transferred across the barrier at different rates. Pre- and postoperative studies on one patient with small ventricles reproduced accurately the curves described by Laurence for communicating and normal cerebrospinal fluid pathways as demonstrated by using phenolsulfonphthalein dye. The majority of our patients had large ventricles, however, and the dilution of the tracer substance was so great as to render the results equivocal. We know nothing of glucose or urea transport.

21. Correlation Between Intestinal Absorption and Mucosal Histology in Patients Apparently Recovered from Celiac Disease. CHARLES U. LOWE, M.D.; MARY O. CRUISE, M.D.*; BERNARD DORAY, M.D.*; CYRUIS E. RUBIN, M.D.,* and LLOYD L. BRANDBORG, M.D.* University of Buffalo School of Medicine and Children's Hospital, Buffalo, and University of Washington School of Medicine, Seattle.

The diagnosis of celiac disease rarely causes alarm, since the illness is usually not fatal. Evidence, however, is accumulating to make a casual approach of this disease unwarranted, and there are data to suggest that adult nontropical sprue occurs commonly in subjects who had a malabsorption syndrome in childhood. In most instances the ingestion of a "celiac" type diet, the virtue of which now is presumed to be an absence of gluten, was followed by a disappearance of symptoms. The natural history of their illness is unclear, since with the disappearance of symptoms such patients are rarely followed by physicians until signs of sprue supervene. The perfection of techniques for peroral biopsy of small-bowel mucosa has made it possible to observe the characteristic lesion of the villi which is the same in both early celiac disease and adult nontropical sprue. Although data on the absorptive defect and the mucosal lesion in celiac disease and sprue are available, it is unknown whether patients undergo cytological and physiological remission during the years when they are asymptomatic. The present report attempts to answer this question by comparing clinical course, intestinal absorption, and mucosal histology in appropriate subjects.

Five children with celiac disease observed for from 6½ to 15 years, were subjected to small-bowel biopsy at a time when stool complaints were absent, health was superficially good, and diet normal. The original diagnosis of malabsorption was made in all cases by appropriate laboratory determination and in three subjects by long-term fat balance studies. All five patients demonstrated conspicuous response to a gluten-free diet, though none consumed this after stools became normal.

Microscopic examination of the biopsy specimen in all patients showed abnormal small-bowel mucosa, despite an absence of clinical complaints. It seemed reasonable to assume that the mucosal lesion rather than the absence of complaints represented the true state of the illness. Compatible with this was the consistent significant depression of bone age (5/5) low level of iron in the serum (3/5) and abnormally low vitamin A absorption (5/5). The oral glucose tolerance test was usually normal (4/5).

These data suggest that celiac disease may result in a mucosal lesion which persists despite disappearance of symptoms. Evidence for activity of the disease was obtained not only by biopsy of intestine but also by a flat vitamin A absorption curve, retarded epiphyseal maturation, and a low level of iron in the plasma. It seems probable, on the basis of these data, that the prognosis of celiac disease is not good. The mucosal lesion may be congenital in origin, and refractory to therapy. The duration of consumption of a gluten-free diet may affect the clinical course, but no data are available to indicate that this regimen may produce either an indefinite remission or permanent cure.

Discussion

DR. AUGUSTA MCCORD, Rochester, N. Y.: I would like to add that Dr. Rubin has been working with us too on celiac cases which we have followed for many years, and the results we have obtained are very similar to those just reported.

JOHN W. GERRARD, Saskatoon, Canada: Dr. Lowe and his colleagues are to be congratulated on this study, which shows that the mucosal defect in celiacs brought up on normal diets persists. The work confirms clinical studies undertaken in Birmingham, England, by me and my colleagues, when a careful reevaluation of so-called recovered celiacs on normal diets showed, in fact,

* By invitation.

that none had fully recovered biochemically. We do not yet know whether the mucosal defect persists in the treated child—we have one patient who has been on a gluten-free diet for three years and she still has an abnormal jejunal mucosa—but we do know this, that the young celiac put onto a gluten-free diet makes a much more rapid recovery than the adult who has had an established steatorrhea for many years; it is possible that the jejunal mucosa may actually become more "atrophic" if the child is allowed to remain untreated, on a normal diet. Because the mucosal and biochemical defects persist in the untreated child it is important to establish the diagnosis of celiac disease in any one patient on a firm basis, and it is as important to examine the jejunal mucosa in a suspect celiac as it is to analyze the sodium and chloride content of the sweat in a child thought to have cystic fibrosis of the pancreas.

DR. CHARLES V. LOWE: I would support what you said. I tried to indicate that part of the problem in the literature, and even more important in clinical practice is that children are labeled "celiacs," whatever that means, and there is neither appropriate laboratory study nor history to support this diagnosis. I would suspect that a mucosal biopsy will be able to differentiate clearly the group of patients who have celiac disease with a characteristic mucosal abnormality and an appropriate clinical history from those with temporary or even long-term diarrhea but without celiac disease.

DR. CHRIS P. KATSAMPES, Rochester, N. Y.: Dr. Rubin biopsied four of our patients, and three of them had severe lesions. In the fourth case, however, the biopsy showed a normal intestinal mucosa. This patient, an 18-year-old boy, was diagnosed as 2 years of age when he had a flat vitamin A absorption curve and large amounts of fat in the stool. We reevaluated him 14 years later, in 1956, and the vitamin A absorption curve was still abnormal and he still had an increased amount of fat in the stool.

A month ago, however, his vitamin A curve was just within normal limits. His stool fat was also within normal limits. There are reports in the British literature on postmortem material which indicate that the pathological lesions may be patchy in distribution. We wonder if we can assume in this one case that perhaps this boy does have patches of normal and abnormal intestinal mucosa since he still has clinical symptoms of celiac disease although he appears to be biochemically normal.

DR. LOWE: I can't answer your last question, Dr. Katsampes, I'm sorry.

The technique of obtaining intestinal mucosal biopsies is a very intriguing one. We have a new tool for the investigation of infants and children, as well as adults, with the malabsorption syndrome or other conditions in which failure to thrive may be related to defects in the mucosal absorbing surface.

Dr. Cyruis Rubin, of Seattle, called this technique to the attention of both Dr. Diamond and me when he visited Boston in December, 1957. We started a collaborative study much in the same way as Dr. Rubin has done with other pediatric centers where patients with the malabsorption syndrome are seen. It is obvious that celiac disease is sufficiently rare that no one clinic can provide sufficient material to yield statistically significant results in a short-term study. I should like to show the youngest baby studied, namely a 14-month-old infant with celiac disease, who was on the wards at the time. The second photo shows this same youngster six months later. In spite of the remarkable improvement in this baby's clinical condition, the mucosal lesion remains essentially unchanged. The next two slides show photographs of the duodenal mucosa during the acute phase and six months later. Ten other patients were studied, eight of whom were diagnosed as having celiac disease. This interval between the acute phase of the disease and the time of biopsy was relatively short (less than 1½ years in most instances), and the children were still on a gluten-free diet. The lesions, at this time, were similar to the lesions Dr. Lowe showed in patients in whom the interval extended over a much greater period of time.

The duodenal intestinal mucosal biopsy may offer assistance in difficult diagnostic problems in infancy, and we are pursuing this types of study at the present time. One can differentiate cystic fibrosis of the pancreas from celiac disease, but there are much simpler methods of making the distinction. I should like to show two additional slides, that of an infant with a malabsorption syndrome in whom a malrotation of the cecum was demonstrated. In years gone by some of our surgeons would have recommended a surgical procedure to fix the cecum. In this particular instance we persuaded our surgical colleagues to refrain and this youngster was treated with a celiac diet and showed a very dramatic response, as illustrated in the photograph. After recovery, the intestinal biopsy was obtained and the mucosa showed a lesion which Dr. Rubin described as characteristic of severe celiac disease. In view of what has already been said, it seems clear that this lesion had been present at the time of the acute illness.

There are a number of important questions that must be answered. What is the specificity of the mucosal lesion in celiac disease? How early does it occur? Is it present before clinical symptoms appear? The other point concerns the reversibility

of the lesion, and, from Dr. Rubin's experience of over 30 patients with the malabsorption syndrome, it seems unlikely that the anatomical lesion is a reversible one.

DR. LOWE: I did not understand whether the child with malrotation is considered to have celiac disease or whether the mucosal lesion is secondary to recurrent or chronic intestional obstruction. I think the distinction is important because in our hands children with recurrent intestional obstruction, such as that due to malrotation and bands, do not respond well to a gluten-free diet.

Could I ask Dr. Shwachman to clarify that point?

DR. SHWACHMAN: I think all of us who have had experience in the differential diagnosis of celiac disease have seen children with this condition in whom the radiologist may demonstrate a malrotation of the cecum. In years gone by competent surgeons, of the caliber of Dr. Ladd and Dr. Gross would, on occasions, attempt to correct this condition. The clinical response to the combined effect of medical, dietary, and surgical therapy, was often very satisfactory, and much of the credit was given to the surgical procedure. On the other hand, we wondered if the malrotation in itself was responsible for any of the symptoms; certainly there were no signs of obstruction. My purpose in showing this child is to try to clarify a very difficult and confusing diagnostic problem and to point out that this patient had celiac disease with a concomitant malrotation, which perhaps had very little to do with the symptomatology. Inasmuch as her lesion is present now three and a half years after the acute illness, one may be justified in stating that this lesion had been present much earlier.

I think you missed my point completely about the age at which a tube can be passed. My point in mentioning this is to indicate that in dealing with celiac disease we are dealing with infants and small children, and that we now have a technique which could readily be used in studying the acute stage of the disease. Serial biopsies in one patient can provide very significant information, and I know of no infant so far reported in the literature where serial biopsies during the acute and recovered phase has been reported.

DR. LOWE: We have no information on small-bowel x-ray examination done at the time of biopsies, so I cannot answer your question.

DR. BENJAMIN KRAMER, Brooklyn: I wonder how the histological changes correlate with the small-bowel studies by roentgenological examination. We have picked up several cases of granulomatous enteritis by small-bowel studies which were verified subsequently at operation.

DR. LOWE: We have no information about small-bowel intestinal examination at the time of biopsies, so I don't think I can answer your question.

DR. M. DAVIDSON, New York: I would like to make two points if I may, the first in regard to Dr. Gerrard's comment. One of the most important additions to the diagnostic armamentarium for cystic fibrosis has been the sweat test. This has been due not only to the inherent academic value of this still unexplained finding, but also because it has minimized the need for the rather arduous duodenal intubations. At best these are difficult when one is seeking enzymatic aspirate. The current technique in its application to celiac disease requires the passage of a more difficult semirigid tube than for simple aspiration. In addition, bleeding has been reported with this tube. I would therefore like to insert a word of caution regarding its widespread use in view of its having recently become commercially available and suggest that for the time being it still remain a research tool. It is one thing to report the experience in the hands of as excellent an endoscopist as Dr. Rubin and another to suggest general usage.

The second comment I would like to make is not intended to detract from Dr. Lowe's very excellent presentation. In spite of the fact that children with proved celiac disease often make a remarkable improvement clinically within a week of the institution of gluten-free diet therapy, it takes them a relatively long time to demonstrate such improvement from balance studies and other laboratory determinations. Dr. Katsampes story about the 18-year-old patient is an illustration of the length of time it takes. Dr. Lowe's patients were all on normal diets at the time of biopsy and during the early period had also been given minimal amounts of unidentified complex carbohydrates. It is quite possible that on a strictly gluten-free diet over a long period of time some of these mucosal lesions might disappear. I wonder whether Dr. Lowe would comment on the statement made in the abstract that this particular mucosal lesion might be congenital in origin, in view of some of the statements I have just made?

DR. LOWE: I think you raised two points. One has to do with the danger of the biopsy and the other with the permanence of the lesion.

Dr. Rubin and his colleague Dr. Brandenborg have now done, I think, between 700 and 1,000 biopsies. The last 300 have been done with a modified Shreiner tube. This modified tube has led to no apparent complications. It is their feeling that there is no danger with the use of the modified tube. The earlier tube apparently did lead to some complications.

You raise a second question, and I think a very valid one. If a patient were maintained on an

appropriate diet, let's say for 15 or 18 years, would the lesion disappear? My answer has to be that I don't know, and the literature contains insufficient information to offer an answer. So far as I know no one has remained on this diet sufficiently long to give this information. When adults with nontropical sprue are put on a gluten-free diet, there is a long period when no response can be observed, and even when response occurs, the mucosal lesion does not disappear. This still doesn't answer the question you raised. Maybe only time will be able to provide a reply.

DR. JOHN M. CRAIG, Boston: I wonder how widely spread in the upper gastrointestinal tract the lesion of sprue may be. Two of the slides shown by Dr. Lowe appear to be from the duodenum, since they contain the glands of Brunner, and one of the biopsies shown is from the prepyloric area of the stomach, since there are branching glands at the base of the lamina propria. The second slide shown by Dr. Shwachman also appears to be duodenum. Would Dr. Lowe tell us if the characteristic changes can be recognized in a duodenal biopsy?

DR. LOWE: All of the illustrations presented represented small-bowel biopsies. The extent of the mucosal lesion is unknown. I think I pointed out in our presentation, that autopsy material in this disease is extremely difficult to find, and hence is insufficient to answer the question. We have none in our hospital and, as I remember, in Boston there were only two children with celiac disease who had been autopsied. What we attempted to do in our biopsies was to obtain one duodenal specimen and one jejunal specimen. We were not always successful.

I would suggest that changes in the duodenum may be sufficiently diagnostic to preclude jejunum. Until we know this for certain, however, we will continue to obtain jejunal specimens.

22. Testosterone-Induced Remission in Aplastic Anemia. NASROLLAH T. SHAHIDI, M.D.,* and LOUIS K. DIAMOND, M.D. Department of Pediatrics, Harvard Medical School and Children's Hospital, Boston. (Published in full in the September issue of this Journal.)

Review of the cases of aplastic anemia seen at The Children's Hospital during the last 20 years revealed that a wide variety of therapeutic agents have been used with no success. Transfusions, vitamin preparations, splenectomy, and corticosteroids have been tried singly or in combinations. For the past 18 months, in addition to steroid therapy and transfusion, some patients with proved aplastic anemia have been treated with testosterone. Rationale for this was based on several experiences. The first patient so treated was a 7-year-old boy who had received 13 transfusions during a six-month period while on corticosteroid. The bone marrow remained markedly hypocellular and fatty. The addition of testosterone proprionate resulted in a slow but sustained reticulocytosis which reached a peak of 14% after three months of therapy. The bone marrow at this time revealed a markedly hypercellular specimen with erythroid hyperplasia. The reticulocytosis resulted in a rise of hematocrit, and the transfusions were discontinued. The continuation of the treatment produced a steady increase of hemoglobin, and after six months of therapy the hemoglobin reached a peak of 14 gm. %. Upon the withdrawal of testosterone and the steroids the hemoglobin as well as the reticulocyte level fell abruptly. A month later the patient was placed on testosterone alone, which resulted again in reticulocytosis. However, since there was no noticeable rise of hemoglobin, it was felt that a hemolytic component might be present, and erythrocyte survival studies showed a chromium half-life of 17 days. The addition of corticosteroid resulted again in a rise in hemoglobin. Repeat survival studies now showed a chromium half-life of 21 days. These findings may indicate that, while testosterone has an erythrogenic action of the bone marrow, the addition of the corticosteroids increased the erythrocyte survival.

At the present time five other patients are under testosterone therapy. One has shown a similar remission; the others have had clinical improvement with prolongation of transfusion interval and bone marrow regeneration as evidenced by reticulocytosis.

Although this is a small series of patients with aplastic anemia treated with testosterone, the results are so promising in contrast to the almost uniform failure of all

* By invitation.

previous therapy that encouragement for further similar therapeutic attempts seems definitely warranted.

Discussion

DR. NATHAN SMITH, Madison, Wis.: We certainly have enjoyed not only this morning but on several previous occasions talking with Dr. Shahidi about his most interesting approach to this problem.

I would like to hear from others regarding the experience Dr. Shahidi referred to as to the prognosis of aplastic anemia. Of 40 patients three had spontaneous remission, the remainder going on to a fatal outcome. It would be my impression, although I have no figures available at this time to support this impression, that a somewhat less gloomy prognosis might be in order in recent years with better supportive therapy available.

I am sure many of us would like to hear something regarding the complications that might be associated with this therapy. Likewise, I would like to have Dr. Shahidi enlarge a little bit on the nature of the marked improvements in platelets and in leukocytes that he reported.

In closing, I would just like to mention that, following Dr. Shahidi's suggestion approximately a year ago, we have treated two patients and are beginning therapy of a third patient with testosterone and cortisone. In the two patients we have treated, we have seen a very positive response in the leukocytes, and a slow but very definite response in the hemoglobin and red cell levels. The platelet counts have not risen very markedly in our two patients. They have gone from very low levels up to about 80,000. However, these patients under steroid therapy have been asymptomatic as far as bleeding is concerned.

DR. NASROLLAH T. SHAHIDI: In relation to Dr. Smith's question concerning the prognosis of aplastic anemia, although a better management during recent years has helped these patients through many difficulties and has increased their life expectancy, the incidence of fatal outcome has remained the same. Dr. J. A. Wolff, who has recently reviewed, I believe, some 300 cases of aplastic anemia, has found survival of about 3% (*Ped. Clin. North America*, May, 1957). These results correlate closely with our data.

With regard to the side-effects of testosterone therapy, several aspects should be considered. Acne, flushing of the skin, and mild hirsutism occurred in all our patients, two to three months after therapy. The deepening and hoarseness of the voice, which occurred mainly in male patients, followed the dermatologic signs. The changes in external genitalia and growth of pubic hair appeared from one to three months after therapy. Being concerned about a more serious complication, namely, premature closure of epiphyses, we have taken roentgenograms of the wrists of these patients before testosterone therapy and at two- to three-month intervals while they were on the medication. We have not observed noticeable change in bone maturation. For example, the following two slides show the roentgenograms of the wrist of the first patient at the age of 8 years, prior to testosterone therapy, and again at the age of 9 years, after eight months of testosterone therapy. As is seen, in both instances, the bone age correlates closely with the patient's chronological age.

Testosterone therapy also seems to have beneficial effects on myelopoiesis in our patients. The rise of platelets and polymorphonuclears, although not as dramatic as that of red blood cells, was in certain instances quite remarkable. For instance, in Patient 2, whose initial hemogram showed a white count of 820/cu.mm. with 16% polymorphonuclears, after six months of therapy the white cells rose to 5,000 with 50% polymorphonuclears. In Case 3, whose platelet count was in the range of 30,000 prior to institution of testosterone therapy, adequate platelet levels were found after four months of medication.

DR. JAMES A. WOLFF, New York: At Dr. Shahidi's suggestion we have treated three patients with aplastic anemia with testosterone, one of whom has made a very effective response as far as the hemoglobin is concerned. Treatment for about eight to nine weeks was required before this response was obtained. It would appear from the data presented that at least some of Dr. Shahidi's patients have also required a considerable period of treatment before response was obtained. Our patient made a slower granulocytic response. Granulocytes did not rise for about four months after the start of treatment. There has also been a late but appreciable rise in platelets to levels similar to those mentioned by Dr. Smith, namely, about 90,000.

I wonder whether Dr. Shahidi has any idea as to why this very slow response takes place and why our patient has also failed to show the expected type of reticulocytosis following therapy. Our patient has had only a slight rise in reticulocytes, although this has been fairly sustained.

I would also like to ask Dr. Shahidi to comment further concerning the patient who failed to respond to oral testosterone but apparently made a response to intramuscular testosterone. The second patient we treated has been treated entirely with intramuscular testosterone from the beginning in very large dosage. In a period of two months, she has failed to respond. I wonder what other experiences he has had with intramuscular testosterone?

DR. SHAHIDI: The slow response to testosterone therapy in these children may be explained in a variety of ways. First of all, aplastic anemia is different from the specific deficiency of either iron deficiency or pernicious anemia, where the supply of a specific agent such as iron or vitamin B_{12} produces prompt reticulocytosis. In aplastic anemia, where the bone marrow defect is mainly quantitative, a quick response to therapy would seem unlikely. In addition, testosterone does not seem to be a specific agent for erythropoiesis. Furthermore, in the patient receiving testosterone, we have noticed a slow improvement in the bone marrow before any noticeable change is observed in the peripheral blood. In regard to use of an intramuscular preparation of testosterone, our experience is limited. We avoid intramuscular preparations in these patients because of the possibility of local reactions, such as infection or hematomas. Intramuscular testosterone should be limited to younger children, who tend to chew or swallow the sublingual tablets. Methyltestosterone in large doses, or fluoxymesterone, when ingested have been reported to increase erythropoiesis in patients with cancer of the breast and with myeloid metaplasia. These drugs also should be tried on small children. The erythropoietic activity found in the postmortem examination of the bone marrow in the first patient who succumbed to simultaneous occurrence of infection and hemorrhage could not be attributed solely to i. m. testosterone, since this patient was started on this medication only 10 days prior to his death.

DR. KRIVIT, Minneapolis, Minn.: Following Gilbertson and Kennedy's demonstration that testosterone caused an increase in number of red cells and amount of hemoglobin, we treated two children who had aplastic anemia. In each, testosterone was given in a dosage of 25 mg. daily for three months. Cortisone compounds were not given simultaneously. No significant change in any of the hematologic parameters occurred.

I would like to know if you have studied the urinary amino acid pattern in these children? It appears probable that metabolic deficiencies might aid us in differentiating the types of aplastic anemia who do and do not respond to testosterone.

DR. SHAHIDI: We have not looked for amino acids in the urine.

DR. SANFORD L. LEIKIN, Washington, D. C.: I wonder if any patients with pure red-cell anemia have been treated with this regimen. We have tried two patients with this condition without observing any improvement.

DR. SHAHIDI: We have treated a patient with congenital hypoplastic anemia with testosterone without any response. I believe more of these patients should be tried on testosterone before the results can be reliably evaluated.

DR. DORIS HOWELL, Durham, N. C.: At Duke we now have six children on a combination of steroid-testosterone therapy for their aplastic anemia. The first was one of the successfully treated children mentioned by Dr. Shahidi. Another on the same treatment appears to be starting to respond after four months of therapy. The remaining four have been treated in a different fashion in that we have utilized the Squibb product, Deladumone (90 mg. testosterone enanthate and 4 mg. estradiol valerate per cubic centimeter), because we hoped to get the added anabolic effect of estrogen with the testosterone and also to counteract if possible the osteoporotic effect of long-term steroid therapy, which has caused us so much trouble in our long-survival leukemia patients. This product must be given intramuscularly, but a 2 cc. dose every three weeks appears to be equivalent to the oral methyltestosterone used on the first two patients. Of this latter group of four, two have not been on therapy a sufficiently long time to evaluate response, but the other two, who have both received four months of therapy—12 mg. of Aristocort daily and 2 cc. of Deladumone every three weeks—are just now beginning to show a reticulocytosis, and bone marrow examination of one of them shows nests of red cell in the marrow. In all cases no response was seen before two months of therapy, and most of the children have required three to four months before any significant regeneration appeared.

DR. ROBERT KLEIN, Pittsburgh: I think one thing that might be noted is that probably the reason the bone age did not advance rapidly is that this effect of testosterone could be inhibited by the cortisone or other corticoid administered at the same time. I wonder what will happen after these agents are withdrawn for a year or so.

Is it possible, now that you are maintaining general health somewhat better, that some complications are being avoided, and that these are spontaneous remissions after a long period of time?

DR. SHAHIDI: One of our patients who had a satisfactory remission under testosterone therapy has been off this medication now for more than five months without any relapse or complication. His general condition is as satisfactory as that of the patient who had spontaneous remission.

23. Masculinization of Female Infant Associated with the Use of Stilbestrol During Pregnancy. ALFRED M. BONGIOVANNI, M.D.; ANGELO M. DI GEORGE, M.D.,* and MELVIN M. GRUMBACH, M.D.* The Children's Hospital of Phila-

* By invitation.

delphia; St. Christopher's Hospital for Children, Philadelphia, and Babies' Hospital, New York.

Four infants and children have been studied, all apparent females with clitoral hypertrophy and labioscrotal fusion (in two), unassociated with the adrenogenital syndrome due to congenital adrenocortical hyperplasia. None of the mothers had evidence of virilizing disease. Although the administration of androgen per se and progesterone (Progestin) to the pregnant woman have been reported as causes of masculinization of the fetus, no such hormones had been employed in any of these instances. Stilbestrol alone had been employed because of previous abortions or miscarriages. The urinary 17-ketosteroids were normal in all patients. Oral mucosal smears revealed female-type nuclei in all. There was no progressive virilization in any. Exploratory operation in one revealed the presence of ovaries. Vaginograms in two were consistent with female internal genital organs.

Previous embryologic experiments (Greene et al. and Moore) have produced paradoxical masculinization of female offspring following the administration of estrogens to the rat and opossum. In the frog (Witschi) estrogens, in large doses, produced masculinization of genetic females in conjunction with adrenal hyperplasia. Although a direct effect of estrogens in producing masculinization cannot be disproved, this appears unlikely as the explanation for the changes observed in these four patients. Perhaps adrenal androgens are produced in response to the administration of estrogens during pregnancy in certain rare "susceptible" fetuses. Further speculations on the significance of this association will be presented. These observations, in conjunction with previously reported effects of androgens and progestins on the fetus, call for greater thoughtfulness in the use of various hormones during pregnancy.

Discussion

DR. JOHN J. HUTCHINGS, San Francisco: We have seen three similar patients with some degree of masculinization, and these mothers have no history of ingestion of any substance during pregnancy. The mothers do, however, have a history of difficulty with fertility and repeated miscarriages and bleeding during pregnancy. I wonder if the factors which operate might be factors in the maternal environment connected with difficulty in fertility rather than with hormone administration.

DR. ALFRED M. BONGIOVANNI: Your point is well taken, and I'm sure there are cases which cannot be traced to hormones. Three of our four mothers did not have an extraordinary history of infertility or abortion. They really had very little reason for receiving stilbestrol, and this often happens. The fourth one was perhaps a little unusual. I do wish to reiterate that this phenomenon of fetal masculinization after maternal estrogen administration is an "old story" for the experimental biologist.

DR. JUDSON J. VAN WYK, Chapel Hill, N. C.: Recently an 11-year-old girl was admitted to our urology service for surgical correction of labial fusion. There was slight clitoral hypertrophy as well. The mother had threatened abortion at the 12th week of pregnancy and had received 75 mg. of stilbestrol for one day and 25 mg. daily thereafter. Apparently we were not as perceptive as Dr. Bongiovanni, since we assumed that she had received Progestin, even though no history of this could be elicited. This may be another case to add to your series.

I should like to propose an alternative hypothesis to that suggested by Dr. Bongiovanni. Older patients with gonadal dysgenesis typically have scanty pubic hair and low 17-ketosteroids before treatment with estrogens. The administration of estrogens promptly results in an elevation of the 17-ketosteroids to normal levels and the pubic hair becomes more abundant. Albright postulated that the secretion of androgens by the adrenal at the time of adolescence is due to an additional trophic hormone, perhaps luteotrophin. Might the paradoxical effects which you have observed be the result of estrogens stimulating the adrenal cortex through the modality of luteinizing hormone?

DR. BONGIOVANNI: I have no comments on this experience.

DR. ARTHUR ROBINSON, Denver: It may be of interest that we had a female pseudohermaphrodite whose mother had received Progestin during pregnancy. This child had had a sibling who was also a female pseudohermaphrodite associated with the mother's having received Progestin. For this rea-

son, we were interested in the possibility of some chromosomal anomaly existing. We obtained a biopsy of this baby's skin and looked at her chromosomes. This baby has 46 normal chromosomes with two normal-looking X chromosomes.

DR. ROBERT ULSTROM, Minneapolis: We have also seen the adrenogenital syndrome on two occasions associated with the administration of steroids during pregnancy. On a third occasion, a child whose external appearance was like those shown today had bilateral orotestes, I wonder if your patients have had gonadal biopsies, since they could represent true intersexes.

DR. BONGIOVANNI: Only one of these patients has had gonadal biopsy.

DR. EDNA H. SOBEL, New York: Possibly the ingestion of stilbestrol during pregnancy can, in some individuals, lead to an alteration in adrenal or even ovarian function with an increase in the secretion of androgenic compounds. Such an effect would probably not be reflected in the measurement of total "17-ketosteroids" excreted in the urine. We do know that 17-ketosteroid excretion during pregnancy is actually much lower than in the nonpregnant state, and that 20-ketosteroids make up the bulk of the Zimmermann-reactive material extracted from the urine. Probably you have not had the opportunity to fractionate and identify the steroids excreted by the mothers of these patients during the pregnancy. Information on this point might help to elucidate the mechanism of the virilization, but of course one would not advocate stilbestrol therapy during pregnancy in the light of your observations.

DR. BONGIOVANNI: Yes, unfortunately it was well after the pregnancy in each instance.

DR. CLAUDE J. MIGEON, Baltimore: If Dr. Wilkins had been able to attend this meeting, I am sure he would have liked to discuss the present paper. I hope that my comments will agree with his own views.

In Dr. Wilkins series (*J. Clin. Endocrinol.* 18:559, 1958) on the masculinization of the female fetus associated with administration of Progestin during gestation, there were also three cases of masculinization of the female fetus where the mother had received no hormonal therapy.

In view of this latter finding, it might be necessary to determine the frequency of this urogenital malformation of the newborn in cases where the mother has received no hormonal treatment and in cases where the mother has been given estrogens during gestation before incriminating the estrogen therapy as a direct or indirect cause of the masculinization of the fetus.

DR. BONGIOVANNI: I agree with everything that Dr. Migeon has said. One reason for giving this presentation was to call attention to this so that it might be studied further and so that we might keep our eyes open for some of these things. I also have the feeling that these various studies in nurseries should include the matter of hormones administered during pregnancy, and the other thing that Dr. Grumbach, Dr. Di George and I are concerned about, is the possible effect of these hormones on the gonads. We didn't go into that, and we don't really know how many infants who don't show the gross malformation may have had damage to their gonads.

24. An Experimental Approach to the Study of Adoption. JULIUS B. RICHMOND, M.D.; LEONARD HERSHER, PH.D., and A. ULRIC MOORE, PH.D.* Department of Pediatrics, College of Medicine, State University of New York, Syracuse, N. Y., and Behavior Farm Laboratory, Cornell University, Ithaca, N. Y.

The adoption process has been of considerable interest to pediatricians and child welfare workers. Although there are approximately 100,000 adoptions per year in the United States, little experimental data has been available concerning adoptions. In order to study this process experimentally we have turned to an animal population (domestic sheep and goats) in which manipulation of certain experiences may be accomplished.

Four different adoptive relationships are being studied: (*a*) ewe adoption of a lamb not its own; (*b*) ewe adoption of a kid; (*c*) doe adoption of a kid not its own, and (*d*) doe adoption of a lamb. There are approximately equal numbers in all groups.

Within 24 hours after delivery, the mother's own offspring is taken from her and another kid or lamb put in its place. If the mother does not accept the substitute immediately, she is restrained in an immobile stanchion in order to curtail her ability to butt or to harm the lamb or kid.

Both mother and young are penned together in small completely closed stalls whether the mother is initially restrained or not. Under these conditions the young attempt to suckle the foster mothers, and almost all mothers accept and nurse the foster young after varying lengths of time

* By invitation.

in restraint. Films will be shown to illustrate this "successful" adoptive process.

Differences in mother-young relationships between inter- and intraspecies adoptions will be reported, as well as differences between foster family interaction and normal (control) family interaction.

Quantitative results will be presented concerning the character of maternal contact, protection, nursing, and discrimination of young. Illustrations of such behavior will be presented on film.

Discussion

DR. SAMUEL KARELITZ, New Hyde Park, L. I. N. Y.: I think we've had many examples of mothers being given babies other than their own for nursing. To the best of my knowledge there has been no problem until the parents have been told that they have the wrong babies. Adaptation is quickly formed, and there seems to be no difficulty between the human infant and the foster or temporarily adopted parent.

Dr. Richmond said that the observations made in this study are in no way applicable to the human. We do, however, have a situation in adoption practice which lends itself to similar study. More and more interracial adoptions are occurring throughout the world and particularly here in the United States. We are bringing in to the United States for purpose of adoption Greek, German, Canadian, Chinese, and Koreans. These and some of our American children of different shades of color and race, Negro-white, Indian (American), Mexican Indian-white, are being taken into homes of white parents. It will be a fascinating experiment to observe how quickly they will be integrated with the parents of different color and with their local social groups. Just as in the animal study, I believe that it will ultimately succeed. I am very grateful to Dr. Richmond for presenting this very fascinating study.

DR. JULIUS B. RICHMOND: I can't listen to Dr. Karelitz's comments concerning our work without expressing our appreciation to him for his very long and active interest in the human adoption process and the significant efforts that he has made toward the improvement of adoption standards.

The comments concerning the introduction of a strange infant to a human mother are interesting. We would again want to emphasize caution concerning inferences from our studies to the human situation. There are infinitely more variables in the human situation. Most of these, of course, cannot be controlled, and this is why we have moved toward the use of animal populations which we can manipulate more readily for experimental purposes.

From these studies we develop our observational skills and develop hypotheses and methods which can prove to be very valuable in observations of human mothers, observations which we as well as many others have in process.

The matter of interracial adoptions is, of course, a most interesting one. But again I wouldn't want to draw any inferences from these studies to the human situation. We feel that it's too big a jump for us to make.

DR. DEWITT C. BALDWIN, Boston: I recall a report some years ago of the reactions of native mothers to their babies following delivery under anesthesia by our military personnel. A large percentage of these mothers rejected their offspring in the belief that the babies were not their own, since they had not been conscious during delivery, and had been separated from them during the immediate postpartum period. It required a strenuous program of education and persuasion to enable these mother-child relationships to get their belated start.

I believe our understanding of this important area of pediatrics can gain immeasurably from the use of animal experiments of the type reported here.

DR. RICHMOND: I want to thank Dr. Baldwin for his remarks. I don't have any familiarity with the study he mentioned. It is, of course, known to psychotherapists who see patients in long-term therapy that some women state they were not sure they received their own baby because they were not conscious at the time the baby was delivered. They may report anxiety about this over a long period of time. We know too little about the reasons for variation in response of human mothers. In our studies we hope it will be possible for us to observe in the next year and a half or two how some of these adopted young, in turn, mother their own young as they mature. We do have the opportunity of observing successive generations and this may enable us perhaps to make some inferences about early mothering experiences and their implications for the ultimate development of maternal capacities.

DR. ARTHUR H. PARMELEE, Los Angeles: I'm sure that Dr. Richmond is aware of the work of Dr. Lorenz with imprinting in birds in which the genetic factors seem to play a large part. Certain highly bred black hens accepted only black chicks, whereas less carefully bred hens or barnyard hens would accept not only chickens but ducklings and sometimes mice.

I only mentioned this in order to point out that when you work with animals such as the goat and sheep, imprinting becomes less likely and less distinct. Then, if you progress to man, there is even less of our brain committed to innate releasing

mechanisms. I also wonder if it is wise to spread human interaction apart into small facets, and if it isn't more correct to study this in a more global manner in contrast to what Dr. Richmond has suggested. Many simple observations have been made in an adoption agency, such as that of a mother who is a very active mother receiving a placid baby and being somewhat disappointed in the placid baby but ultimately adjusting to this, and a mother who is herself placid receiving a very active baby and finding it difficult to adjust. I think we have so many cultural and other factors to deal with that we might get into difficulty breaking these human reactions down into segments.

DR. RICHMOND: Thank you, Dr. Parmelee. We are, of course, aware of the work of Lorenz and others and have had occasion to discuss some of this material with Dr. Lorenz when he was here last fall. Imprinting is certainly a very important phenomenon and much discussed by the ethologists in recent years. I want to make it clear, however, that what we are talking about is imprinting on the mother and not imprinting on the young. The ethologists are often concerned with both simultaneously. I think your points are well taken concerning the significance of the central nervous system. Our own conceptualization concerning this problem falls somewhere between the ethologists and the learning theorists. As physicians, we are biologically oriented; thus we think of behavior as emerging from the interaction of genetic factors (central nervous system endowment) with enviroment (or experiences) rather than focusing exclusively on one or the other.

I think the point you have made concerning looking at global patterns of mothering is pertinent. I mentioned looking at more discreet aspects because research in this field has moved forward all too slowly, perhaps in part because we have been preoccupied with global patterns, with the result that quantitative studies of some of the factors which go to make up the global pattern have not been investigated specifically. Studies like this are just very small steps into a field of research which has been relatively undeveloped, and we can only emphasize the need for experimental studies.

25. Teratogenesis: Embryonic Versus Placental Injury. ROBERT L. BRENT, M.D., PH.D.* Department of Pediatrics, Jefferson Medical College, Philadelphia. Introduced by Gilbert B. Forbes.

Although placental factors may play a role in congenital malformations, their importance in the human is unknown. This is not surprizing since it is difficult to affect the placenta experimentally without also affecting the maternal organism and the embryo. One of the exceptions to the latter statement is by the use of low energy x-irradiation. With this tool, it is theoretically possible to irradiate the placenta alone or the embryo alone. Previous investigators have demonstrated that shielding of the embryo when irradiating the mother was not teratogenic to the embryo (Brent). Other experiments have shown that irradiation of the embryonic site while shielding the mother, as compared with irradiating the entire pregnant mammal, resulted in a comparable incidence of malformations (Wilson and Brent). This investigation attempts to characterize the indirect effect of placental irradiation on fetal growth and survival.

Twenty-eight pregnant rats were anesthetized and laparotomized on the 12th day of gestation, and the pregnant uteri were exteriorized. Irradiation was then administered to the embryonic sites in one of several manners.

The animals were killed four days later and were examined for fetal mortality, fetal weight, and congenital malformations. The fetal mortality figures were most surprising; for the control embryos and the embryos whose placenta were irradiated had mortality figures which were statistically indistinguishable. This occurred in spite of the fact that 400 r was used as the radiation dose. At term, 400 r results in an LD_{100} when given at the 12th day of gestation in the rat.

Effect of Irradiation of Embryonic Sites

Manner of Irradiation	Mean Weight, Mg.	Per Cent Mortality
1. Irradiation of the complete embryonic site	516.1	56.7
2. Irradiation of the placenta alone	663.8	3.8
3. Irradiation of the embryo alone	531.8	28.3
4. Irradiation of one-half the placenta and one-half the embryo in the same embryonic site	567.4	33.9
5. Control embryonic sites consisted of those sites which had manipulation comparable to groups 1-4 but were shielded during irradiation	668.3	13.3

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Furthermore, the control group and the irradiated placenta group yielded fetuses whose mean weight could not be statistically distinguished. Thus it was found that the placenta was very resistant to irradiation and that placental irradiation did not either increase fetal mortality or decrease fetal growth. The comparative results of the other groups is given. These data along with the incidence of malformations will be discussed.

It then appears that irradiation of a pregnant rat which results in congenital malformations, fetal mortality, or growth retardation is due neither to an indirect toxin from the mother or to placental dysfunction but is a direct effect of the irradiation on the embryonic tissue. It is to be stressed that this does not mean that the placenta plays only a minor role in the human congenital malformation problem; for such a generalization could be grossly in error. It should be pointed that errors can be made in utilizing information from one experiment or from several clinical cases to explain the human malformation problem.

26. Thrombocytopenia and Intestinal Bleeding in Premature Infants. EUGENE KAPLAN, M.D., Baltimore City Hospitals, Baltimore.

A continued outbreak of neonatal thrombocytopenia and intestinal bleeding has been under investigation in a large premature nursery. After the initial discovery of thrombocytopenia in several infants with transient mild intestinal bleeding, 261 infants in this nursery were followed with platelet counts and careful clinical surveillance for bleeding over a period of 18 months. Thrombocytopenia (platelets less than 100,000/cu. mm.) was found in 75 infants, in 40 without bleeding. Clinical bleeding was noted in 61 infants, in 35 associated with thrombocytopenia. This bleeding was limited to the intestinal tract in 53 infants and more generally distributed in 8 infants. The intestinal bleeding was characterized by the presence of varying small amounts of fresh blood on the surface of or mixed with normal fecal material. It began after the third day of life, and lasted only several days in most instances. There was no evidence of proctitis, rectal fissures, or other clinical disturbances in this group. When accompanied by thrombocytopenia (29 of 53 infants), this thrombocytopenia usually preceded and persisted beyond the period of bleeding and was not associated with any other hematologic abnormality. The syndrome was observed in six sets of twins, in three of whom bleeding and platelet patterns coincided; in three sets one twin was affected. The incidence varied inversely with the birth weight; thrombocytopenia and/or clinical bleeding occurred in 75% of 35 infants weighing less than 1,400 gm., 50% of 92 infants weighing between 1,400-1,800 gm., and 25% of 134 infants weighing more than 1,800 gm.

The appearance of additional infants with thrombocytopenia, intestinal bleeding, or both still continues in this one premature nursery after an 18-month period, although similar disturbances have not been noted in a comparable study of 100 infants from other local nurseries. A survey of environmental and clinical factors has to date yielded no clue as to etiology.

27. The Significance of the Respiratory Distress Syndrome in Premature Infants. WILLIAM ALLEN BAUMAN, M.D.* Babies Hospital and Department of Pediatrics, Columbia University, New York. Introduced by Rustin McIntosh.

Neonatal respiratory distress in premature infants is recognized as a phenomenon associated with a poor prognosis. Because of its serious consequences and because of current attempts to prevent or remedy this condition, it is important to define the syndrome more clearly. Hence a study of 201 premature infants whose birth weight was less than 2,001 gm. was undertaken. Five physical abnormalities of the syndrome were tallied as a "retraction score" in order

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to obtain a quantitative definition of respiratory distress.

In those infants who had breathing difficulty before 24 hours of age, there was a greater case fatality rate than in the group without dyspnea. Moreover, the smaller babies had a greater incidence of distress, died sooner, and more frequently had hyaline membrane in their lungs than did the heavier babies. The incidence of respiratory difficulty diminished from 37% at age 6 hours to 19% at age 24 hours.

Examination of the relationship among each of the five components of the "score" and the presence of hyaline membrane supported the contention that expiratory grunt and intercostal retractions on inspiration are frequent forerunners of death with pulmonary hyaline membrane. These correlations were unlikely to have occurred as a result of chance alone ($p<0.05$).

In those subjects with significant dyspnea the crude case fatality rate was 60% in the first 7 days of life, whereas only 10% of those without distress died during this interval. Of those with dyspnea before death, half had hyaline membrane deposition, whereas only 1 in 10 of those with normal respirations had this pathologic finding.

Hence by use of a quantitative method for grading the dyspnea of newborn premature infants a definitive syndrome emerges for which morbidity, mortality, and anatomical postmortem findings may be described.

28. The Use of Intramuscular Iron in the Prophylaxis of the Iron Deficiency of Prematurity. S. L. LEIKIN, M.D.* Research Foundation, Children's Hospital of Washington, Washington, D. C. Introduced by Roland B. Scott.

The premature infant is much more vulnerable to iron-deficiency anemia because his total body hemoglobin available for use is smaller and his growth rate is usually greater than that of the full-term infant. Recently intramuscular iron has been found to be effective in supplying the human organism with large quantities of parenteral iron for hemoglobin synthesis. It was felt worth while to compare the prophylatic regimens of oral iron versus that of intramuscular iron. Twenty-nine premature infants were studied in the nursery during the first two weeks after birth, with blood counts, serum iron determinations, and bone marrow aspirations for sideroblast counts. Twenty premature infants were injected with intramuscular iron, and the remainder were given oral iron.

The intramuscular iron group received an average of 430 mg. of iron per infant over a period of several days. The infants in the oral series received a minimum of 1.0 mg. per kilogram per day until one year of age. Serial hematologic studies were done at three-month intervals on both sets until one year, when all the original studies were repeated. No dietary restrictions were placed on either group. The mean birth weight of both groups was similar. There was a difference in the mean hemoglobin of these two groups in favor of the oral group at time of the initial study.

It was observed that there was a significant difference between these two groups at 3, 6, and 9 months, the group receiving the intramuscular iron having a higher mean hemoglobin than the other set of infants. At one year of age the mean weights and the hematologic picture of both sets were similar. No serious side-effects were noted in either group.

It is felt that there are several advantages in the use of intramuscular iron for the prophylaxis of iron deficiency anemia of prematurity, particularly in a poor socioeconomic population.

29. Body Water in Relation to Nutrition of Premature Infants. B. M. KAGAN, M.D.; NATALIA FELIX-BALKCOM, M.D.*; J. F. TURNER,*† and JOYCE JESSAMY, B.S.* Department of Pediatrics, Cedars of Lebanon Hospital, Los

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† Deceased.

Angeles County Hospital, and the University of California at Los Angeles.

The weights, total body water, and extracellular water were measured in premature infants before and after a controlled period of isocaloric feedings of human milk and a cow's milk mixture.

Premature infants fed isocaloric amounts of high-protein, low-fat, high-ash cow's milk gain more weight than those fed human milk. At one time it was thought that this difference might be due to the higher protein content of the cow's milk mixture. Studies we reported in 1955 suggested that this difference in weight gain was probably related more closely to difference in ash intake and therefore to difference in water retention.

The current study demonstrates that the greater part of the difference in weight gain was due to retention of water in excess of the expected percentage based upon correlated data. The difference in weight gain over a 21-day period between the two groups currently under study was 6.29 gm. per kilogram of body weight per day. The difference in the increase in total body water was 5.51 ml. per kilogram of body weight per day. The total body water per unit of body weight among those fed the human milk decreased, whereas among those fed the cow's milk mixture it increased. Of the water compartments, the direction of change was as follows. Infants fed human milk lost extracellular water and gained some intracellular water. Among the infants fed the cow's milk mixture there was an increase in both compartments.

There was no significant difference in the gains in dry weight—whether the infants were fed human milk or cow's milk preparation. The t values are significant to better than the 0.01 level for the differences in weight, total body water, and extracellular water. For intracellular water, the difference was significant to the 0.05 level.

30. Acidosis in Premature Infants Created by Lactic Acid Milk. HERBERT I. GOLDMAN, M.D.*; NORMAN B. SCHELL, M.D.*; SAMUEL KARELITZ, M.D., and ELI SEIFTER, PH.D.* Long Island Jewish Hospital, New Hyde Park, N. Y.

Increased absorption of fat and calcium, and increased resistance to infection have, in the past, been attributed to the use of acid milks. This led us, in a previous study, to assess the usefulness of lactic acid milk in prematures. We found that lactic acid milk produced poor weight gain, apathy, and pallor in a group of premature infants, and the present study was undertaken to investigate the mechanism of the poor results observed.

Methods.—The present investigation was performed as four separate studies. During each of these, observations were made on a number of premature infants fed a lactic acid milk mixture (experimental infants), and on an equal number of infants who received a half skimmed milk mixture, and who served as controls. The infants in the control and experimental groups were selected to be similar in age and birth weight.

Both the control and experimental infants received the half skimmed milk mixture prior to the study period. At the onset of the study period, the experimental infants were changed to the lactic acid milk, while the control infants remained on the half skimmed milk mixture. The study period lasted 7 to 10 days, and during this time all infants received 120 cal/kg/day, and 150 cc/kg/day. The infants were weighed, and blood samples were collected immediately prior to the onset and at the conclusion of the study periods.

Results.—1. Weight Gain: The infants fed the acid milk gained much less weight. The average gain for 18 control infants was 13.6 gm/kg/day, and the comparable average for 18 infants fed the lactic acid milk was 5.6 gm/kg/day.

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2. Carbon Dioxide Content (Blood): There was a fall in the CO_2 of the experimental infants during the study. The average for 12 control infants was 19.1 mEq. per liter at the onset, and 20.4 at the conclusion of the study periods. The comparable averages for 12 experimental infants was 19.6 and 14.8 mEq. per liter.

3. pH (Blood): There was a fall in the blood pH of the experimental infants. The average for 12 control infants was 7.38 at the onset and 7.40 at the conclusion of the study periods. The comparable averages for 12 experimental infants were 7.39 and 7.25.

4. Urine Lactic Acid: There was a marked increase in the urinary concentration of lactic acid in the infants receiving the lactic acid milk formula.

5. Blood Lactic Acid: The control values for blood lactic acid ranged from 5.5 to 24.3 mg. %. The values obtained while lactic acid milk formula was being fed were slightly higher, with a maximum value of 35.7 mg. %. The data, however, are inadequate to support any definite conclusion.

It is concluded that the particular lactic acid milk used in this study produces an acidosis in some premature infants with failure to thrive. The lactic acid used is a racemic mixture of the *d* and *l* forms. The probable mechanism of the acidosis is discussed. It is suggested that lactic acid milks not to be used as routine feedings in premature infants.

31. The Significance and Prevention of Iron-Deficiency Anemia in the Premature Infant. JOHN A. JAMES, M.B.,* and MOLLIE A. COMBES, M.D.* Department of Pediatrics, The University of Texas Southwestern Medical School, Dallas, Texas. Introduced by Edward L. Pratt.

It has been previously shown that the incidence of serious infections during the first year of life is two to three times greater in the ex-premature than in the full-term infant. Marked iron-deficiency anemia is commonly found in association with these illnesses; both anemia and infections are commoner in babies of low birth weight. Agreement is general that iron supplementation is essential in the growing premature infant, but the optimal time and method of administration is still a matter of dispute. In the present study an attempt has been made (*a*) to investigate a method of preventing iron-deficiency anemia in premature infants; (*b*) to study the pattern of erythropoiesis in the presence of an unlimited iron supply; (*c*) to determine whether preexisting iron deficiency may increase the incidence of infections.

About 50 randomly selected premature infants weighing less than 2,000 gm. received "prophylactic" intramuscular iron (250 mg. of Imferon) during the neonatal period; an equal number received no supplemental iron until the hemoglobin level fell to about 7 gm. %. Selected hematologic studies, and the clinical course, development, and health record of these babies have been followed until the first birthday.

Higher hemoglobin and hematocrit levels were observed by 7 to 8 weeks of age in those infants receiving intramuscular iron, and these were maintained throughout the first year, whereas some of the untreated infants, who defaulted from the Clinic and therefore did not receive oral iron, became dangerously anemic. No untoward effects of the intramuscular iron were observed. There was no difference between the two groups in the number of hospital admissions or clinic visits for respiratory infections or diarrheal disease.

These results suggest (*a*) that exogenous iron may be utilized for hemoglobin formation by the premature very early in life (the significance of this finding in relation to the available iron stores is being investigated); (*b*) that moderate iron deficiency does not predispose to respiratory or gastrointestinal infections; (*c*) that iron deficiency anemia in premature babies can be prevented by the "prophylactic" use of intramuscular iron. This approach should be

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of considerable value in premature well-child clinics where follow-up is uncertain and oral iron medication is unlikely to be obtained or given in adequate amounts.

32. Motions of the Pharynx and Larynx with Aeration of the Lung at Birth. JAMES F. BOSMA, M.D., and JOHN LIND, M.D.* Department of Pediatrics, University of Utah College of Medicine, Salt Lake City, Utah, and Department of Pediatrics, Karolinska Institute, Stockholm, Sweden.

Initiation of respiration was observed by series of roentgenograms obtained sequentially at intervals of 2-6 per second. Technically adequate observations were made on 23 newborns, all of whom were born at term of normal labor, with little or no maternal anesthesia, and of cephalic presentation. They were apparently free of anomaly or neurologic impairment, and established respiration in normal manner.

Roentgenographically evident initial aeration of the lung was associated with patterned actions of the pharynx and larynx. The most distinctive of these actions was that of glossopharyngeal respiration, essentially similar to this performance employed as alternate mode of respiration in poliomyelitis subjects having extensive paralysis of trunk musculature, or to the glossopharyngeal respiration seen as part of focal brain stem seizures in infancy. As observed in these newborn infants, glossopharyngeal respiration was usually initiated by pharyngeal distention associated with abrupt inspiratory filling of the lung. There is then essentially a swallow motion carrying a "bolus" of air into the trachea rather than into the esophagus. This is associated with motions of constriction within the trunk and evidences of an increase in intrathoracic pressure. The motions of gasping were observed as a variant of glossopharyngeal respiration, in which pharynx actions preceded the abrupt extension at the neck.

The alternative pattern of pharynx and larynx motions at this time was that familiarly observed in the modulation of respiration. In this, the pharynx walls and arytenoid portion of the larynx moved in relation to the comparatively stable reference base of hyoid bone and thyroid cartilage. The commoner action within this pattern was that of a total occlusion of pharynx and larynx, which was distinctive of this occasion. There was also more discrete closure or partial closure at the larynx or the upper pharynx.

These performances were coordinated with the respiratory actions of the thorax, including the large inspiration at the initiation of glossopharyngeal action and the expiratory actions associated with closure of pharynx and larynx in either of these patterns of their performance.

It is apparent from these radiographic observations that the whole of the respiratory organization is involved in initial aeration of the lung and establishment of respiration. At this critical physiological transition of respiration, the infant has available unique motor actions of the upper respiratory way.

These performances of the upper airway are barely discernible by external observation, but the method of cervical auscultation distinguishes adequately between swallow-glossopharyngeal respiration and the abrupt sounds of opening and closing of the upper airway and the higher-pitched sounds of partial occlusion. These performances should be included in common clinical evaluation of respiratory performance of the newborn infant.

33. Significance of the Infant's Cry. SAMUEL KARELITZ, M.D.; RUTH F. KARELITZ, B.A., M.A.,*† and LAURA ROSENFELD, B.A., M.A.* Department of Pediatrics, Long Island Jewish Hospital, New Hyde Park, N. Y.

Believing that the infant's cry is governed in large measure by the central nervous system, we have attempted to study the

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cry of normal newborn infants and periodically at 2 and 5 days, at 1 month, 3 months, 6 months, 9 months, 1 year, and at shorter intervals up to the age of 3 years. Other vocalizations, such as cooing and gurgling, and early speech sounds, are also recorded at intervals, beginning at three to four months. Kattell and other suitable tests have been performed. We now have high-fidelity magnetic tape recordings of about 80 infants through the first 15 months and about 20 more to 9 months. All of the first group and many of the second group have had psychological testing. In addition, we have recordings of eight sets of twins, one set of triplets, and several small premature infants, as well as about 50 abnormal infants, e. g., cases of Mongolism, cerebral palsy, Tay-Sachs disease, etc.

At the present time we are able to demonstrate the changes in the vocalizations of normal infants and to correlate them with their development. It is evident to the ear that the vocalizations of brain-injured children are different from those of the normal child. It takes more stimuli to provoke crying. The cry is less sustained and of shorter duration, and the pattern is one of interrupted efforts, as compared with the more rhythmic continuous cry of the normal infant stimulated in the same way—by a flick of the finger on the bottom of the foot.

While clinical observation is usually revealing of the mentally damaged child, in some instances it is revealed earlier by the cry. Examples of normal and abnormal cries will be played, and the significance of these observations in the possible detection of deafness, cretinism, and brain damage will be discussed.

34. The Effect of Protein Intake on Renal Conservation of Water in Young Infants. HENRY L. BARNETT, M.D.; CHESTER M. EDELMANN JR, M.D.,* and VASSILIKA TROUPKOU, M.D.* Department of Pediatrics, Albert Einstein College of Medicine, New York.

The optimal dietary content of protein for the feeding of young infants has not been established. Observations on infants fed diets of different protein content have demonstrated some differences in their rate of growth, but no detectable differences in their general health, development, or well-being. On the basis of immature renal function, with special regard to the degree to which osmotically active solutes are concentrated in the urine, it has been suggested that lower protein feedings, providing a minimal renal osmolar load, offer a larger margin of safety with regard to water balance, should the infant decrease his normal intake or develop abnormal water losses. Recent observations reported elsewhere (Edelmann, Troupkou, and Barnett, *Fed. Proc.* 18:40, 1959) have demonstrated that the degree to which the young infant concentrates the urine varies considerably with the levels of intake of protein and water. Following high-protein feeding, the maximal concentration of urinary solutes during hydropenia was observed to approach adult levels. Thus, during prolonged dehydration, the increased solute load of a high-protein diet was found to obligate little or no additional water for excretion. Further paired observations have been carried out on infants fed first high (6 gm/kg/day) then low (2.5 gm/kg/day) protein diets. Following the oral administration of water loads of 17-23 ml/kg. of body weight, food, and water were withheld for periods up to 14 hours, during which measurements were made of rates of urine flow and concentrations of urine electrolytes, urea, and total osmotically active solutes. As expected, the infants demonstrated a prompt water diuresis, lasting two to three hours, after which the rates of urine flow either stabilized at low levels or demonstrated a further gradual decline. After the period of water diuresis infants previously fed a low-protein diet attained slightly lower rates of urine flow than were

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observed in the same infant after ingestion of a high-protein diet. However, the rates of flow following either diet differed so slightly and were so low that the difference in total urine volume was never more than a few milliliters, an amount which could not be considered significant in terms of total body water conservation. Moreover, despite total urine output for the entire period of observation of a maximum of 15 ml. in excess of the amount given in the water load, the infants regularly demonstrated a significant degree of dehydration, as evidenced by clinical status and body weight loss. It is therefore concluded that the relatively limited ability of the infant to withstand the stress of complete food and water deprivation does not lie in a deficient renal response, but rather in large, continuing insensible water losses, in view of which the slightly increased amount of renal water obligated by previous high-protein feeding cannot be considered clinically important. These data do not permit prediction of the effect of continued feeding of diets of varying protein content during periods of inadequate intake or excessive loss of water. Observations on these points are in progress.

35. Cerebrospinal Fluid Glutamic Oxalacetic Transaminase and Lactic Dehydrogenase Activity in Newborn Infants.

MIRIAM LENDING, M.D.*; LAWRENCE B. SLOBODY, M.D.; MARTIN L. STONE, M.D.,* and JOAN MESTERN.* Department of Pediatrics, New York Medical College, and Flower and Fifth Avenue Hospitals, New York.

There is an increase in activity of cerebrospinal fluid glutamic oxalacetic transaminase (GOT) and lactic dehydrogenase (LDH) in various neurological conditions in adults, e. g., cerebrovascular accidents, cerebral thrombosis, convulsions. This suggested the study of these enzymes in newborn infants with suspected intracranial pathology.

The cerebrospinal fluid and plasma activity of GOT and LDH was studied in 50 normal newborn infants and in a series of 30 who had a maternal history of complications during gestation and delivery, e. g., toxemia, placenta previa, diabetes, prolapsed cord, prolonged labor and/or infants who presented such clinical findings as low Apgar score (below 3 at 60 seconds after delivery) or convulsions, cyanosis, respiratory difficulty in the nursery.

Cerebrospinal fluid was obtained by lumbar puncture and blood from femoral venipuncture. GOT and LDH determinations were performed using the method of Karmen and Wroblewski and LaDue, respectively.

The range of cerebrospinal fluid GOT activity was from 3.7 to 19.0 units/ml/min., average 8.7 units, a 94% mean increase over that we have reported previously in the normal newborn infants. The range of plasma GOT activity was from 13 to 95 units/ml/min., average 44.3 units, a 20.1% mean increase over the normal controls. Cerebrospinal fluid LDH activity ranged from 31.6 to 855.0 units/ml/min., average 121.5 units, a mean increase of 276.2% over the normal controls. Plasma LDH activity ranged from 480 to 2,740 units/ml/min., average 1,410 units, a mean increase of 21% over the normal newborn infants. The greatest increase in cerebrospinal fluid and plasma enzyme activity was observed in the newborn infants having frequent convulsions.

These results have correlated with those we have observed in puppies with experimental convulsions and hypoxia. Analysis of the data suggests that changes in cerebral cell membrane permeability plays a major role in producing this increase in cerebrospinal fluid enzyme activity rather than actual cerebral cell lysis, although increased permeability of the blood-cerebrospinal fluid barrier may also be a factor.

The significance of the increase in these cerebrospinal fluid enzyme activities can only be established by follow-up for several

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years of both normal and abnormal infants. It would be essential to correlate the neonatal cerebrospinal fluid enzyme activity and clinical status with the possible subsequent development of mental retardation, cerebral palsy, epilepsy, and behavioral changes.

36. Severe Neutropenia in a Newborn Infant with Shigella Alkalescens Sepsis. JOSEPH P. ROSSI, M.D.* and IRA K. BRANDT, M.D.* Department of Pediatrics, Yale University, New Haven, Conn. Introduced by Milton J. E. Senn.

The complete absence of circulating neutrophils associated with sepsis due to Shigella alkalescens has not been previously reported. The case to be described was further complicated by the presence of agglutinins in the mother's serum against the father's and the infant's leukocytes, but the significance of this finding could not be fully evaluated.

The patient was a white male infant, the product of a normal, full-term, spontaneous delivery. The antepartum course was uneventful, and at birth the infant appeared normal. On the second day of life he had several mild seizures and at 72 hours he developed intermittent cyanosis, tachypnea, and splenomegaly, but he remained afebrile, and icterus was not noted.

At this time he was found to have a granulocytopenia, and by the sixth day this had progressed to complete absence of neutrophils from the peripheral blood. Later, there was an absolute increase in monocytes which reached a peak on the 11th day of life. At this time neutrophils reappeared, and as their number increased there was a concurrent fall in monocytes until by the 16th day both were present in normal concentration. Anemia did not occur.

Nose, throat, and blood cultures taken on the third day of life revealed a pure growth of Shigella alkalescens. The administration of penicillin and chloramphenicol was begun and continued until 16 days of age.

On the sixth day of life leukoagglutinins could not be demonstrated, nor was there any inhibition of starch granule phagocytosis when a mixture of infant's serum and donor white blood cells was used. The L. E. preparation was negative.

The bone marrow on the seventh day was predominantly myelocytic. There was some increase in young monocytes but no increase in myeloblasts. Another bone marrow preparation at 29 days of age was normal.

The intramuscular administration of 5 units of aqueous corticotropin on the 10th day of life did not result either in the appearance of neutrophils in the peripheral blood or in a fall in the absolute eosinophil count.

The infant made an uneventful recovery, and his absolute neutrophil count has remained within normal limits for the past nine months.

The neutropenia was believed to be secondary to endotoxin release from the Shigella alkalescens sepsis. However, the possibility of the presence of leukoagglutinins at the height of neutropenia could not be definitely excluded by the above-noted procedures. Further studies performed when the infant was 8 months old revealed that the mother's serum agglutinated both the baby's and the father's leukocytes. Unfortunately, samples of the infant's serum obtained during the episode of neutropenia were not available for additional testing, so that one cannot state with certainty whether or not an immune mechanism contributed to the severe neutropenia in this case.

37. Studies of Hemoglobins at Birth with Follow-Up Observations During Infancy. VIRGINIA MINNICH, M.S.*; JAMES K. CORDONNIER *†; BARBARA JONES, M.D.,* and W. GENE KINGBERG, M.D.* Departments of Internal Medicine and Pediatrics, Washington University

* By invitation.

† Senior medical student.

School of Medicine, St. Louis. Introduced by Alexis F. Hartmann Sr.

The incidence of abnormal hemoglobins was studied in the cord blood of 200 infants (110 Negro and 90 Caucasian); in addition, changes in the concentration of the abnormal hemoglobins recognized were followed during the first few months of the postnatal period. Paper, agar, and starch block electrophoretic techniques were used.

Ten of the babies (nine Negro and one Caucasian) were found to have a "fast" hemoglobin component (2.3% to 12.4% of the total) which had an electrophoretic mobility on starch block electrophoresis (pH 8.6) greater than Hgb A and slightly less than Hgb J. The component, when eluted from the starch, was relatively resistant to alkali denaturation. This property plus the fact that it disappeared from the blood in 6 to 150 days, suggested that it might be another form of fetal hemoglobin. Hemograms done on only 4 of the 10 babies at birth were normal except for <1.0% to 10% target cells and a reticulocytosis of 11.4% in one. In two of these and two others there were associated abnormalities; one each with Hgb D, Hgb S, hereditary elliptocytosis, and thalassemia trait (the last two blood diseases were diagnosed at 3 months of age). Except for <1% to 10% target cells in the peripheral blood, five babies were normal in all respects at 3 months of age. One infant was lost to follow-up.

Hgb S was detected on agar electrophoresis in the cord blood of 14 Negro babies in a concentration of from 1.7% to 8.5%. With metabisulfite, 0.9% to 13% of the cells assumed a sickled form. These infants all appeared to have sickle-cell trait, as Hgb A was observed in all hemolysates by starch and agar electrophoresis. The presence of Hgb A on follow-up of nine babies at 1 to 6 months of age was confirmed. Five newborns with Hgb S were not reexamined. The Hgb S determined at monthly intervals in four infants reached maximum concentration of 30% to 45% within three to six months.

Hgb C comprised 5.5% of the total hemoglobin in the cord blood of one Negro infant (starch block and agar electrophoresis). It increased in amount to 24% of the total at 3 months, and to 32.5% at 5½ months of age.

Hgb D was present at birth in two Negro infants (26% and 28% of the total Hgb). Maximum values were obtained somewhat more quickly than for Hgb S or Hgb C: in 35% at 1½ months in one baby, and 36% at 2½ months in the other child.

38. Observations on Fetal and Newborn Bilirubin Metabolism. WILLIAM J. WATERS, M.D.,* Department of Pediatrics, College of Medicine, State University of New York, Syracuse, N. Y. Introduced by Julius B. Richmond.

In studying jaundice in the newborn, and particularly that associated with hemolytic disease of the newborn, the apparent variability in production and tissue handling of bilirubin has been rather striking.

At birth, jaundice is rarely discernible and serum bilirubin levels are rarely excessive. Some have explained this as representing placental clearance in utero. Clinical and laboratory data will be presented suggesting that this may not be a factor.

It is further suggested that the conversion of hemoglobin to bilirubin may proceed slowly in utero. Laboratory data from a case of severe hemolytic disease of the newborn will be presented. This case, despite prompt and repeated replacement transfusions, showed a sustained rise in serum bilirubin, suggesting a precursor pigment pool in the tissues at birth with subsequent conversion.

Finally it becomes apparent that jaundice in the newborn represents an imbalance between bilirubin production (hemolysis of RBC's, ? other) and tissue function (substrate(s) and enzyme(s) concentration as well as liver excretory capacity). These variables and the factors influencing them will be further discussed in relation to the

* By invitation.

implications for therapy of newborn jaundice and the prevention of bilirubin encephalopathy.

39. Full-Term Newborn Infants Kept in the Prone or Supine Position in the Nursery; the Incidence of Crying, Diaper Rash, and Self-Inflicted Excoriations. H. G. KEITEL, M.D.*; R. COHN,*† and D. HARNISH.*† Department of Pediatrics, Jefferson Medical College and the Episcopal Hospital, Philadelphia. Introduced by Irving J. Wolman.

It has often been noted that infants cry less when they are placed in the prone position, and most physicians favor this position to facilitate the drainage of mucus or regurgitated food. However, it is the custom in many nurseries to keep newborn infants in the supine position to avoid the risk of smothering which allegedly occurs in infants kept in the prone position. Since there seemed to be a lack of specific information on the effect of position on neonatal morbidity, a study was initiated to evaluate the effect of maintaining newly born infants in either the prone or the supine position.

Newly born infants were assigned in rotation to either the prone or the supine position immediately on admission to the nursery. The infants were kept side by side and the type of diaper and bedding, the time and type of feeding, use of diaper medications, and frequency of changing diapers were controlled in both groups of infants. Daily rounds were made between 7:30 and 9:15 a. m., at which time the infants were undressed and carefully examined under a bright light. "Crying" rounds preceded the physical examination.

Over one-third of 281 infants developed diaper rash and/or scratch marks during their nursery stay (Table). Knee erythema was limited almost exclusively to infants in the prone position but was only rarely severe enough to be considered clinically significant. The frequency and severity of diaper rash and scratch marks was one and a half to two times greater in infants kept in the supine rather than the prone position. These differences were statistically significant.

The frequency of crying was about twice as great in the infants kept in the supine position. When the position of the infants who were crying was reversed, over one-half of the infants in the supine position stopped crying when they were placed in the prone position. Only an occasional infant in the prone position stopped crying when placed in the supine position.

The incidence of pyoderma, breast and umbilical cord erythema, toxic erythema and regurgitation, were not significantly different in the two groups of infants.

Infants were also placed on either their right or left side but this study proved unsatisfactory since most of the infants rolled to either the prone or supine position.

* By invitation.

† Senior medical students at the Jefferson Medical College.

Incidence of Crying, Diaper Rash, and Excoriations in Prone and Supine Positions

	Day of Life					
	1	2	3	4	5	6
Crying						
Babies on back, %.....	14.6	20.5	32.0	42.2	51.8	42.1
Babies on stomach, %.....	9.7	8.5	17.6	13.7	16.0	12.7
Diaper rash						
Babies on back, %.....	0	0	9.4	28.1	38.6	43.9
Babies on stomach, %.....	0	0.8	0.8	10.3	28.0	30.9
Scratch marks						
Babies on back, %.....	14.6	24.2	23.4	27.4	21.9	22.8
Babies on stomach, %.....	9.7	10.2	19.9	19.7	14.0	12.7

In our opinion, dermatoses, and particularly diaper rash and scratch marks, are the most frequent cause of morbidity in the new-born nursery, exceeding in frequency regurgitation and intolerance to food. Members of the nursing service who observed this study and who previously had placed newborn infants only in the supine position, now state that they prefer to keep infants in the prone position.

40. Comparative Study of Human Milk and a Soya Bean Formula in Infant Nutrition. SAMUEL J. FOMON, M.D.* Department of Pediatrics, State University of Iowa, Iowa City. Introduced by Wallace W. McCrory.

In many of the technically underdeveloped areas of the world, the supply of protein of animal origin is seriously limited, and protein malnutrition is common in infants after they are weaned from the breast. Practical measures for controlling protein malnutrition of infants in these areas require the use of vegetable proteins. The study to be reported was performed to compare rate of gain in weight and retention of nitrogen by infants fed a soya bean formula with similar data from studies of infants fed human milk.

Four infants, 4 to 6½ months of age, were studied for periods of 38 to 73 days while receiving ad libitum feeding of a formula in which the protein was derived from soya bean. No other source of calories was provided. The content of protein in the formula was 1.14 gm/100 ml. (6.8% of the calories supplied by protein) and the mean intake of protein by the infants was 1.7 gm/kg/day. The amounts of cystine plus methionine (mean intake, 27 mg/kg/day) and tryptophan (mean intake, 9 mg/kg/day) supplied by the formula were considerably less than the currently estimated minimal requirements for infants.

The rate of gain in weight of the infants was normal, and retentions of nitrogen (15 metabolic balance studies) were at least as great as those of normal full-term infants of similar ages fed human milk.

Because kwashiorkor rarely develops before weaning from the breast, an amount of vegetable protein sufficient to promote rate of gain in weight and retention of nitrogen similar to those of the breast-fed infant is likely to be sufficient to prevent kwashiorkor. The findings of the present study may therefore be of value in consideration of protein allowances for children in several of the technically underdeveloped areas of the world where soya beans, but not protein of animal origin, are available.

41. The Treatment of Diarrhea. CHARLES HENDEE SMITH, M.D. Princeton, N. J. Based on Fifty-Five Years of Private Practice.

Diarrhea is a common disorder in private practice, next after throat and respiratory infections. Hospital cases are mostly severe with dehydration, acidosis, and a high mortality. They have usually been neglected by parents, or badly treated by physicians. Most of them have had milk throughout the illness, and some have had too much electrolyte solution. In private practice most cases are mild and short if properly treated, and the severe form is never seen.

The child with diarrhea can absorb food from the intestine, but that does not mean that a full diet is good for him. Rest of the intestinal tract is just as logical as rest of any other organ with disturbed function.

In private practice diarrhea is treated on many plans. Each physician has a pet treatment, and the results are often bad. The diarrhea does not stop promptly and may go on to the severe form. The commonest treatment is boiled skimmed milk and kaolin pectin mixtures. Skimmed milk requires considerable digestion, is a good culture medium, and carries a high load of protein and electrolyte. Kaolin pectin mixtures are recommended mostly by the manufacturers.

* By invitation.

Textbooks differ widely in their suggestions. Some advise a full or even an increased feeding lest the patient lose weight. (A small loss seems less serious than a continued diarrhea.) Other texts advise "a light diet" without specific directions. One system text gives three different plans in the same volume.

A plan regularly successful and long used by many pediatricians is as follows:

In breast-fed infants: Give water before each feeding and shorten nursing to two to three minutes.

In bottle-fed infants: After first loose stool dilute feedings one-half. After second loose stool stop all milk, fruit, and vegetables. Give only barley or rice gruel and strained orange juice, in definite amounts and at definite hours. Give water freely.

In older children: Give white cereals, rice, toast, crackers, broth, orange juice.

When diarrhea stops allow boiled milk in small amounts and watch for relapse. Other solids are added gradually if improvement continues.

Sulfaguanidine, Sulfasuxidine, Thalamyd give excellent results. More expensive antibiotics are no better, and some of them do more harm than good. Penicillin is of no value, and the benefit from kaolin and pectin is extremely doubtful.

Cultures to determine the organism responsible are difficult and expensive. There are few laboratories equipped to give reliable results. The patient is usually well before the report comes, except in dysentery.

It is high time for some agreement on the treatment of such a common and potentially serious disease. With the confusion of statements in the textbooks the young practitioner may be responsible for many disasters before he learns better—the hard way. The best prophylaxis against severe diarrhea is prompt treatment, with rest of the intestine and effectual medication.

42. An Evaluation of Alkali Therapy in the Management of Salicylate Poisoning in Children. CHARLES F. WHITTEN M.D.*; NIRMALA KESAREE, M.D.,* and JESSE F. GOODWIN, PH.D.* Department of Pediatrics, Receiving Hospital, and Wayne State University College of Medicine, Detroit. Introduced by Wolf W. Zuelzer.

Since only 20% of the salicyl radical is degraded in the body and no means of accelerating this metabolic process is available, specific therapy for salicylate poisoning has been directed toward rapid removal of salicylates from the body. Case reports have indicated that this can be effectively accomplished by exchange transfusion or dialysis.

The remaining 80% of ingested salicylate is excreted via the kidneys in the form of free salicylate and the conjugates of glucuronic acid and glycine. The rate of renal elimination is slow when the urine is acid but can be accelerated by rendering the urine alkaline. Considerable controversy has existed as to the advisability of utilizing this fact in the active therapy of salicylate poisoning. Those opposed have based their prohibitions almost entirely on theoretical grounds and limited animal studies relative to the risk of accentuating the respiratory alkalotic phase. It has also been suggested that the rate of elimination accomplished by alkalinization of the urine is too slow to be of therapeutic value.

It is the purpose of this study to determine whether there is a place for alkalinizing therapy in the management of salicylate poisoning through an evaluation of definitive clinical and biochemical data on a group of children who received sufficient sodium bicarbonate intravenously to establish and maintain an alkaline urine.

The 21 children studied were 4 months to 4 years old and had salicylate levels on admission ranging from 20-84 mg. % (8 above 50 mg. %). After baseline chemical determinations, 20-40 ml. of 7.5% sodium

* By invitation.

bicarbonate was given intravenously over a five-minute period, followed by a constant infusion containing 10 ml. of 7.5% sodium bicarbonate per 100 ml. of ⅓ N saline in 5% glucose administered at a rate of 1-3 ml. per minute. Several children received sodium bicarbonate in 10% mannitol in an effort to ascertain the efficacy of osmotic diuresis in augmenting renal elimination of salicylates.

During at least the first three to four hours of the alkali infusion serial determinations were made of the plasma salicylate level, the per cent of ultrafilterable plasma salicylate, the whole blood CO_2 and pH, the plasma sodium and potassium, the urine pH, and the rate of urinary excretion of sodium, potassium, and the various salicylate fractions.

Our results may be summarized as follows:

1. The rate of elimination of salicylate from the body and the coincident decrease in plasma salicylate level achieved by this therapy was comparable to values reported for exchange transfusion and dialysis.

2. Two children in respiratory alkalosis were treated without untoward effects.

With regard to the potential hazard presented by the respiratory alkalotic phase, two qualifying features are apparent. First, the incidence of respiratory alkalosis in young children when they are actually seen at a hospital is low. Secondly, the plasma pCO_2 is decreased in respiratory alkalosis, hence the amount of sodium bicarbonate that must be administered to achieve an alkaline urine is relatively small.

Our results indicate that alkalinizing the urine through the infusion of sodium bicarbonate is an effective specific therapeutic agent in the management of salicylate poisoning. It has the distinct advantages of universal availability, ease of administration, rapidity with which it can be instituted and the fact that it can be continued over a prolonged period.

43. The Use of Surface Area and Homeostatic Capacities in Simplifying the Physician's Task in Prescribing Fluid, Food, and Drugs. ALLAN M. BUTLER, M.D.; NATHAN B. TALBOT, M.D., and ROBERT H. RICHIE JR., M.D. Department of Pediatrics, Harvard Medical School and Children's Medical Service, Massachusetts General Hospital, Boston.

Because of the recent criticisms of the validity of simplifying the doctor's task by prescribing fluid, food, or drugs on the basis of square meters as compared with age, height, or weight, it seems appropriate to present data supporting the clinical validity and convenience of so doing.

As demonstrated by common practice the prescription of therapy per unit of weight requires a decreasing dosage with increasing weight. Wilson et al. recommended, "on the basis of common clinical experience" that fluid be prescribed by correlating five diminishing milliliter doses per pound with five increasing ranges of age; i. e., varying dosages from 60 ml/lb. to 35 ml/lb. as age increases from under 1 to 11 years or 5 to 110 lb. The fact that this empirical multiple dose method and the single dose of 2,500 ml/sq. meter provide approximately the same fluid intake per patient has been overlooked (Slide I). Also of practical importance is the fact that the margin of safety between upper and lower range over which an individual (not suffering immaturity, illness, or structural defect) can take fluid without overreaching the capacity of the water homeostatic system is much greater than suggested by these authors (Slide I). This is important in explaining why one need not tilt at windmills of theoretical accuracy in prescribing fluid to the majority of patients and how different this margin of safety may be in patients with limitations in homeostatic capacity.

A similar simplification in prescribing diet results for using a single figure for each ingredient per square meter, instead of decreasing amounts per kilogram as

weight increases. Daily dietary allowances of 1,800 calories, 2,500 ml. of water, and 30 gm. of protein per square meter provide the accepted multiple diminishing allowances per kilogram or pound (Slide II).

Possibly even more important in simplifying the physician's task and avoiding serious errors in medication is the application of square meterage to drug dosage.

Varying methods of calculating and varying orienting initial doses of acetylsalicylic acid are used in our teaching pediatric clinics (Slide III). Here, too, the average of the range of the diminishing doses in proportion to weight with increasing age agrees closely with the dosage per square meter.

The ready conversion of dosage shown to be appropriate for adults to doses appropriate for infants and children or vice versa is especially desirable, particularly while the internist and general surgeons who care for the majority of children the world over are confronted with the task of keeping abreast of the ever-increasing number of potent therapeutic agents provided by research and industry (Slide IV).

A table (Slide V) attached to scale or in pocketbook correlating the weight in pounds or kilograms with square meters of eight different-sized subjects permits extrapolation of the weight of any patient from prematures to adults to square meters within the range of significance in prescribing orienting initial therapy.

In conclusion, it would seem that the ± fivefold reduction in figures to be remembered or kept at hand by prescribing food, fluids, or drugs on a square meter basis and the consideration of the individual's need of and tolerance to what the doctor orders has worked to our and our patient's satisfaction for 10 years.

44. Magnesium Deficiency Complicating a Case of Severe Protracted Diarrhea.

H. DAVID MOSIER, M.D.* Department of Pediatrics, University of California School of Medicine, Los Angeles. Introduced by John M. Adams.

Experience in adults has shown that magnesium deficiency may result from losses of gastric juice, which ordinarily contains from 10 to 20 mEq/L. of magnesium. The present observations were made on a 4-year-old boy who developed magnesium deficiency and dramatic clinical manifestations while he was being managed with complete parenteral replacement for a severe malabsorption syndrome. During this period there was continued loss of large amounts of fluid per rectum. At one point a generalized convulsion occurred, which was not responsive to the administration of barbiturates or calcium. Magnesium ion was given intravenously with a slow response. During the postconvulsive period there was marked muscle hyperirritability, and localized myotonia was elicited on tapping a skeletal muscle. There were also fibrillary movements, carpal spasm, a positive Trousseau test, and the presence of a Chvostek response. These signs regressed with continued magnesium administration over a period of several hours. Serum which was taken prior to the administration of calcium or magnesium contained 0.5 mg/100 ml. (0.4 mEq/L.) of magnesium. Further magnesium levels were obtained during the subsequent course. The patient died later owing to other complications. The pertinent findings will be discussed.

This case exemplifies the need to give due attention to magnesium losses in protracted diarrhea. The usual supplementation of 3 mEq/L. of magnesium in commercial polyionic solutions for parenteral use is not adequate to meet the requirement under such circumstances.

45. Hyponatremia in Severe Illness.

P. ROSENBAUM, M.D.*; JOHN L. MOORE, M.D.,* and MARILYN C. HUGHES, B.S.* Department of Pediatrics, Louisiana

* By invitation.

State University, School of Medicine, and Charity Hospital, New Orleans.

The relatively frequent occurrence of hyponatremia as a feature of severe, nonsurgical illness in hospitalized infants and children is emphasized by its recognition in 91 cases during the past 2 years. The 75 cases in whom records were considered sufficient for further analysis, form the basis of this report.

There were 36 (48%) under 4 months of age, 61 (80%) less than 3 years. The illnesses in which hyponatremia was found were varied, many having more than one cause. Included were infections, diarrheal dehydration, central nervous system disturbances, congestive heart failure, uremia, intoxications, malignancy and endocrine disorders. The importance in this population of chronic disease as well as malnutrition, is illustrated by the fact that 54 (72%) were below the 3rd percentile for weight on admission.

An outstanding feature was the finding of severe parenteral bacterial infections in 65 (87%). These included septicemia, pneumonia, meningitis and pyelonephritis. Blood cultures were positive in 24 (32%).

Temperatures, although variable, were subnormal in 34% during hyponatremia. Clinical shock, however, was evident only in a minority; 34 (45%) were clinically dehydrated, 9 (12%) were edematous. Parenteral fluids had been considered necessary in 61 (81%). Sensorium was often disturbed, stupor, coma, or hyperirritability being encountered in 49 (65%).

In the 75 patients 134 instances of hyponatremia (serum sodium less than 131 mEq/L.) were recorded. The distribution of serum sodium values in mEq/L. was: 110-120—18 (13%); 120-125—29 (22%); 125-131—87 (65%).

In 128 serum potassium determinations hyperkalemia was evident in 23%, normokalemia in 68%, and hypokalemia in 9%. Serum osmolarity was generally normal or low; 121 blood pH determinations were recorded in 61 patients. Although all varieties of acid-base disturbance were represented, the majority showed either metabolic acidosis (53%) or were within normal limits (36%). None of these electrolyte determinations, however, seemed to have any predictive value as to ultimate outcome.

Hypertonic saline was given 28 patients in an attempt to correct hyponatremia; 21 (75%) of this group lived; 33 (70%) of the 47 patients who received no hypertonic saline, lived. Further breakdown of these data reveals no differences in the results in the two groups, except possibly in dehydrated patients, in whom 15/16 receiving hypertonic saline survived, whereas 13/18 not treated survived.

46. The Effects of Low-Calcium Diet on the Management of The Severe Form of Hypercalcemia of Infancy. F. X. FELLERS, M.D.*; R. SCHWARTZ, M.D.,* E. B. D. NEUHAUSER, M.D. Department of Pediatrics, Howard Medical School, and the Dutdreu's Hospital, Boston.

In the benign form of hypercalcemia of infancy, the dietary restriction of calcium has resulted in a prompt return to normocalcemia with improvement of the clinical status of the child. Prolonged management has not been necessary. Since the severe form is associated with severe constitutional findings of marked physical and mental retardation, an extensive trial of a very low calcium intake was indicated.

Two infants with the characteristic clinical, chemical, and roentgenological features of this syndrome were given a synthetic formula containing 1.5 to 2.0 mm. of calcium per liter, but otherwise nutritionally adequate, for an 18-month period. Exogenous vitamin D was omitted.

Serum calcium values returned to and remained in the normal range. Persistent hypercalciuria and negative calcium balance failed to result in hypocalcemia. The fecal calcium losses exceeded dietary calcium by 0.5 to 1.5 mM. per day, while the nitrogen and magnesium balances remained positive. After 20 months, one infant showed renal

* By invitation.

conservation of calcium as evidenced by the minimal urinary calcium excretion.

Renal function remained depressed to approximately one-fourth of normal values, although the serum nonprotein nitrogen had originally decreased. Serum phosphorus and alkaline phosphatase values remained unchanged.

Serum vitamin D-like activity as determined by the rachitic rat bioassay and previously reported to be elevated in this disease, has shown a significant decrease in one patient to values now only 10 times the normal, and consistently elevated levels in the other child up to one year after initiation of the diet.

Serial x-ray studies have shown a marked and progressive decrease in the mineralization of the bones with loss of the osteosclerosis and appearance of almost normal bone structure. No evidence of rickets has been noted during this period.

Physical and mental retardation were unaffected by the chemical changes produced by the dietary calcium restriction.

47. Early Versus Late Feeding of Infants of Diabetic Mothers: A Controlled Study. A. J. RUDOLPH, M.B.*; J. P. HUBBELL JR., M.D.*; J. E. DRORBAUGH, M.D.*; R. B. CHERRY, M.A.*; P. A. M. AULD, M.D.,* and C. A. SMITH, M.D. Department of Pediatrics, Harvard Medical School, Boston.

All infants of diabetic mothers delivered in the Boston Lying-in Hospital have until recently been given no food or fluid by any route for at least 48 hours after delivery (Gellis and Hsia, A. M. A. J. DIS. CHILD. 97:1, 1959). It was reported in 1957 (Carrington, Shuman, and Reardon, *Obst. & Gynec.* 9:664) that the oral or intravenous administration of glucose and saline solution within a few hours after birth may reduce both the morbidity and mortality of such infants. Because of this report, during the past 10 months infants of diabetic mothers attending the Joslin Clinic have been placed by random selection in either an early or a late feeding group. The "early" group received 5% glucose and 0.45% NaCl in water (intravenously in those deemed too ill for oral feeding) 30 ml/lb/24 hr. begun three to four hours after birth. After approximately 48 hours, this solution was replaced by dilute formula. Members of the "late" group received their first fluids as 10% glucose in water, or a weak formula, at 48 hours or more after birth; their total fluid intake in the first 24 hours thereafter being approximately 30 ml. per pound.

To date, 56 consecutive liveborn infants of diabetic mothers have been studied, 28 in each group. All have been examined at standardized intervals by a team of observers unaware of the feeding routine. The distribution of significant characteristics and the morbidity and the mortality of the two groups thus selected by chance can be best presented in a short table. This includes measurements of bilirubin † as the most striking comparison which has thus far emerged from the laboratory data.

† This study was performed as part of the Maternal-Infant Health Study Program.

Comparison of Early and Later Feeding of Infants of Diabetic Mothers

	Group Fed	
	Early (28)	Late (28)
Comparability of Groups		
Class of maternal diabetes (Priscilla White Classification)		
B-C (moderate)	9	9
D-F (severe)	19	19
Gestational age less than 36 wk.	12	13
Cesarean section	20	20
Mean Percentage Loss of Birth Weight		
4 hr.	1.2	1.3
24 hr.	4.1	6.3
48 hr.	6.4	10.8
72 hr.	7.0	9.5
Tremulousness	+	++
Clinical Respiratory Distress	16	11
Deaths	4	2
Autopsy Diagnosis of Hyaline Membrane Disease	4	1 (but actively resolving; death on 5th day)
Mean Serum Bilirubin (Indirect) (mg/100 ml.)		
2d-3d day	9.4	12.3
4th-5th day	10.3	15.1

* By invitation.

48. Enzyme Studies in Glycogen-Storage Disease (Hepatonephromegalic Type). RICHARD WAGNER, M.D., and ROSE SPARACO.* Department of Pediatrics, Boston Floating Hospital, and Tufts University School of Medicine, Boston.

Enzymatic activity has recently been studied in two cases of glycogen-storage disease, in one on a biopsy specimen, in the other on autopsy specimens of the liver. Glucose-6-phosphatase was practically missing in the autopsy liver, and markedly below normal in the biopsy specimen, in agreement with the studies of Cori and Cori. From the autopsy enough material was available to carry out further extensive studies which revealed the following results. Experiments on phosphorylase activity in a reaction mixture containing liver homogenate dialyzed for four hours against distilled water, phosphate buffer of pH 7.2, adenylic acid and magnesium ions, showed that during incubation for one hour considerable amounts of a fermentable sugar were formed. This was within the same order of magnitude as in a normal liver. The liver in our patient appeared to be capable of forming in vitro 7.33 gm. of a reducing sugar per hour. Diastatic activity as a source of this sugar could be ruled out; the formation of fermentable sugar in the presence of phosphate buffer exceeded by over 300% that in specimens without inorganic phosphorus.

These observations make it necessary to explain this discrepancy between the diminished phosphatase activity and the formation of large amounts of a fermentable sugar under the above experimental conditions. It is open to discussion whether or not the huge fat and cholesterol content of the liver interferes with phosphatase activity. (The weight of the liver was 2.5 kg., compared with 0.5 kg. of a normal liver of this age group.)

When the time of dialysis was lengthened to 20 hours, the sugar formed during incubation was no longer fermentable. Obviously glycogen degradation reached a standstill at the level of an unfermentable hexose monophosphate.

* By invitation.

49. Experiences with the Administration of Fat Intravenously. S. A. KAPLAN, M.D.*; J. STRAUSS, M.D.,* and A. M. YUCEOGLU, M.D.* Department of Pediatrics, State University of New York, Brooklyn. Introduced by Richard L. Day, M.D.

Lipomul is a fat emulsion for intravenous alimentation which contains purified soya phosphatide as a stabilizer. Many workers have found it to be safe for adults, as has Kaye in the case of children. Spector et al., however, in a series of five children, encountered toxic reactions.

We have explored its safety and utility in a variety of conditions. The dose in this series of 108 infusions in 39 children has been limited to 30 ml. per kilogram per day, given over a six-hour period, which provides 48 calories per kilogram per day. Administration should not be repeated until the serum has become clear.

Following administration, serum cholesterol (12 patients) rose little if at all, and phospholipids by 100 to 200 mg. per 100 ml. The total lipids (reflecting fatty acid concentration) rose from foreperiod levels of 300 to 800 mg. per 100 ml. to 2,000 to 3,000 mg., and returned to normal within 24 hours, but to be on the safe side, we gave infusions no oftener than every second day.

The total experience can be summarized as follows: (*a*) acute diarrhea, 37 infusions to 17 patients; (*b*) chronic caloric deprivation, 16 infusions to 6 patients; (*c*) intestinal fistula, etc., 27 infusions to 7 patients; (*d*) acute renal failure, to minimize endogenous catabolism, 18 infusions to 6 patients; (*e*) minor motor epilepsy, to initiate ketosis at start of a ketogenic diet, 4 infusions to 1 patient; (*f*) bulbar poliomyelitis, 2 infusions to 1 patient; (*g*) encephalitic coma, 4 infusions to 1 patient.

Elevation of temperature to above 101.5 F occurred after 10% of the infusions, but

in many of these instances the patients had febrile illnesses. Among febrile patients, a decline in temperature was often seen. In no instance was there the precipitation of anemia, leucopenia, or hemorrhagic diathesis.

There were nine deaths, none either temporally related or logically attributable to the treatment. The causes of death were thought to have been the following: septicemia (1), diarrhea (3), poliomyelitis (1), croup (1), and renal failure (3). Postmortem examination of patients did not disclose evidence of fatty accumulation in the liver or elsewhere, or of pigment accumulation in the four livers so far studied.

An example of the caloric supplementation possible is that of a 1,800 gm. newborn who had two intestinal operations for atresia during the first 16 days of life. For 9 days, without lipid infusions, only 24 cal/kilo/day could be given. During the next 15 days, during which period the second operation was performed, eight fat infusions raised the average daily caloric intake to 49 calories per kilogram, and body weight was stationary.

50. Influence of Diets High in Essential Fatty Acids. JULIUS POMERANZE, M.D.*; ALTA GOALWIN, M.D.,* and LAWRENCE B. SLOBODY, M.D. Department of Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals, New York.

Total lipids, cholesterol, phospholipids, and lipoproteins have been determined in more than 500 infants and children on the customary diets that are given at the various ages and stages of development. The influence of certain dietary changes on these lipid patterns have been studied.

The purpose of this report is to present the lipid patterns found during the first year of life and how they are influenced by diets high in essential fatty acids (EFA). On the usual diets, serum lipids rise rapidly from relatively low levels at birth to approximate low adult levels by one year of life. During the first year of life, if sufficient amounts of EFA are added to the diet, the lipid levels are found to be significantly lower.

In one group of infants below 4 months of age, corn oil was added to the evaporated milk formula; the total cholesterol levels were lower and alterations appeared in the lipoprotein patterns. In another group fed a prepared milk formula high in essential fatty acids, similar lipid patterns to the above were noted. Removal of the corn oil or the prepared formula high in EFA resulted in a prompt return to the higher lipid levels noted in the control group of infants, who had not been receiving the corn oil or additional essential fatty acids.

After four months of age, infants who were maintained on diets high in essential fatty acids demonstrated an altered lipid pattern, i. e., total cholesterol, lipid, and phospholipid tended to be lower than the control group of infants who were on the customary diets. When these infants were given the same diet as the control infants (not high in essential fatty acids), there was a prompt return to higher lipid levels.

51. Blood Lipid and Protein Studies in Juvenile Diabetes Mellitus. HOWARD S. TRAISMAN, M.D.*; ALVAH L. NEWCOMB, M.D.,* and ROBERT HAMMES, M.D.* Department of Pediatrics, Northwestern University Medical School, Chicago. Introduced by John A. Bigler.

Relatively few reports are available that provide information regarding blood lipid and protein levels in juvenile diabetes mellitus. Because of our interest in this problem, and in the hope that we might gain some clues as to the onset and/or prevention of the degenerative complications, this study was undertaken.

Fifty patients with juvenile diabetes mellitus of varying severity, degree of control, and duration of the disease were studied. There were 24 males and 26 females, ranging from 19 months to 16 years of age. The shortest duration of the disease was 3 weeks, and the longest duration was

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11½ years. The patients were divided into two groups: those whose duration of diabetes was less than five years, and those who had diabetes for five years or longer. There were 15 males and 16 females in the former group, and 9 males and 10 females in the latter group.

The following laboratory tests were done: complete blood count; bleeding, coagulation, clotting, and prothrombin times; 24-hour urine for quantitative albumin and sugar; blood chemistries—fasting sugar, cholesterol, cholesterol esters, phospholipid, triglyceride, total lipid, electrophoresis of lipoproteins, total protein, and A/G, protein electrophoresis, cephalin flocculation, and vitamin A level.

The complete blood count; bleeding, coagulation, clotting, and prothrombin times; and vitamin A levels were within normal range in all our patients. Only one boy had an elevated cephalin flocculation of 3+, and he has a hyperlipemia and hepatomegaly. Quantitative determination of 24-hour urine samples for glucose and albumin were variable for the former, and negative for the latter. The urinary glucose levels were not significant.

The mean blood sugar for this entire series was 228 mg. %. The following serum biochemical studies were within normal limits for total group: cholesterol, cholesterol esters, phospholipid, triglyceride, and total lipid. Protein electrophoresis showed a normal serum albumin and α and α_2-globulin fractions. The β-globulin fraction was elevated, and the γ-globulin fraction was decreased. Lipoprotein electrophoresis was normal for 0, β- and α-globulin fractions. There was no difference between the two groups regarding these blood chemistries. Cholesterol/phospholipid ratio was within normal range for the total series, as well as the groups whose duration of diabetes were under 5 years, and over 5 years.

Mean, standard deviation, standard error mean, standard error difference, and test of significance were done.

Hyperlipemia occurred with diabetic acidosis, and in two young patients with severe diabetes. They will be noted in detail.

The statistics are presented in graph and tabular form.

52. Hyperbilirubinemia in Infants of Diabetic Mothers. P. M. TAYLOR, M.D.*; E. L. BIRCHARD, M.D.*; N. H. BRIGHT, M.D.*; J. H. WOLFSON, M.D.,* and D. W. WATSON, B.S.* Department of Pediatrics, University of Pittsburgh, and Elizabeth Steel Magee Hospital, Pittsburgh. Introduced by Edmund R. McCluskey.

Clinical observation of marked jaundice in several infants of diabetic mothers suggested the need for a planned study to determine the incidence of severe hyperbilirubinemia in such infants. Observations on 33 infants, enrolled in the study at birth, form the basis of this report.

Concentration of bilirubin in the serum was obtained on the third day on all infants and before and after that age as indicated. Cord serum bilirubin concentration was determined on 14 infants. Complete blood counts, including reticulocyte counts, were done daily for the first three days on the majority of the subjects. Studies to rule out hemolytic disease due to isoimmunization were carried out on all severely jaundiced patients. Blood cultures were obtained at the beginning of exchange transfusion during the latter portion of the study. Red blood cell fragility was tested by the hypotonic saline method in seven patients.

The subjects were divided into two groups according to length of gestation: the first group consists of 24 infants delivered at 33-36 weeks gestation; the second group comprises 9 infants delivered after a gestation of 37-38 weeks. Infants of nondiabetic mothers in the appropriate gestational age group admitted to the nursery in consecutive order serve as controls. The general nursery management of the two groups was identical. The same indications

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Bilirubin in Infants of Diabetic Mothers: Classification According to Length of Gestation

	Length of Gestation					
	33-36 Weeks			37-38 Weeks		
	Controls	Infants of Diabetic Mothers	*P*	Controls	Infants of Diabetic Mothers	*P*
Number	41	24		23	9	
Bilirubin, Day 3 Mean ± S. D. (mg/100 ml.)	12.1±4.84	15.6±3.26	<0.001	6.2±4.12	11.2±5.56	0.05>*P*>0.02
Exchange Transfusions (No., %)	8 (19.6%)	11 * (47.9%)	<0.001 (X^2=11.43)	0	2 (22.2%)	<0.01 (X^2=6.55)

* Two of the eleven had two exchange transfusions.

for exchange transfusion were used in the control and study infants. Third day bilirubin values and exchange transfusion rates are compared for the control and study groups in the accompanying table.

The cause of the increased liability of infants of diabetic mothers to develop severe neonatal jaundice is not clear. A markedly elevated hemolytic rate seems unlikely in face of normal to high values of hemoglobin, red blood count, and hematocrit, and normal to low reticulocyte counts during the period under study. Cord bilirubin levels, too, are within normal limits in the study group, as is the osmotic fragility of the red cells of these infants. Septicemia does not seem to play a significant role in the production of this jaundice. Of 10 blood cultures taken, 2 were positive and both were felt to be contaminated. No correlation was found between the severity of jaundice and the severity of maternal diabetes, the route of delivery, the number of nucleated red cells in the infants' peripheral blood, or the presence of neonatal respiratory distress.

These data suggest that maternal diabetes adversely affects liver function in the newborn infant.

53. Comparative Study of the Capacity of Various Commonly Used Solutions to Expand Blood Volume. J. H. PROBST, M.D.*; M. L. TERRY, A.B.*; M. B. MCINTIRE, R.N.,* and N. B. TALBOT, M.D. The Department of Pediatrics, Harvard Medical School and the Children's Medical Service, Massachusetts General Hospital, Boston.

Expansion of vascular volume may be essential to the accomplishment of safe and effective parenteral fluid therapy. Unfortunately, however, clinicians usually are unable to determine their patients' vascular volume status accurately before deciding on the type and volume of solution to be given. Hence it appeared of interest to find out how physiologically comparable doses of various commonly available fluids affect the blood volume and body fluid composition of dehydrated and of normal subjects.

These investigations were carried out on two healthy adult female dogs. They were prepared for the dehydration studies by three days of fasting and thirsting, which resulted in an approximately 15% body water loss, and for the control studies by several days of normal feeding. The experiments were designed to expand vascular volume approximately 15% by the administration of various types of solution, assuming that 5% dextrose in water or multiple electrolyte solution would be distributed throughout the body, that isotonic saline would remain extracellular, and that plasma and whole blood would stay in the vascular compartment.

The manner in which each of these fluids were distributed among the vascular, extracellular, and intracellular spaces during the

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four-hour period of detailed study is described with the aid of charts. Though the total volumes of distribution of the various fluids differed markedly in accordance with their character, all caused a 10% to 25% increase in vascular volume at some time during the initial 90-minute infusion period. The vascular volume of one of the dehydrated dogs increased 40% to supranormal levels while it was receiving dextrose in water. This dog developed signs of circulatory embarrassment; no signs of toxicity were noted in any other subject.

This expansion was sustained for at least two and a half hours after infusion in all the dehydrated dogs and in those normal subjects given saline, plasma, or whole blood. In the normal animals given dextrose in water or multiple electrolyte solution, the expansion was maintained only during the period of infusion.

In conclusion, it would appear that one may under emergency circumstances effectively expand vascular volume with appropriate quantities of any of the fluids used here. With the exception of dextrose-water which proved toxic for the dehydrated dogs, all these fluids apparently were well tolerated both by normal and by severely dehydrated subjects.

54. The Occurrence of a Sex-Linked Coagulation Defect (P. T. C.) and an Autosomal Defect (S-Hemoglobin) in a Family and in a Single Individual. HEYWORTH N. SANFORD, M.D.; GERTRUDE ASROW, B.S.,* and MICHAEL LIMOSANI, M.D.* University of Illinois College of Medicine, Chicago.

We observed in a single family the occurrence of a plasma thromboplastic component deficiency which indicates a sex-linked defect, and the presence of an abnormal hemoglobin which was an autosomal defect. To our knowledge this combination of genetic defects in a single individual has not been reported.

In the investigation of the coagulation defects in two male siblings who were the products of one mother but of different fathers, we observed a third male sibling with cardiac findings and SS hemoglobin. A study was then directed to all the available members of the family for both the coagulation defect and the presence of abnormal hemoglobin.

By means of matching tests and thromboplastin generations (T. G. T.) the coagulation defect was found to be a plasma prothrombin component (P. T. C.) deficiency. The hemoglobin type was studied by means of paper electrophoresis, alkali dematuration, and sickling preparations.

The maternal grandmother, the mother, and a sister of these male siblings were found to have AS-hemoglobin and positive sickling preparations. The mother was also studied to determine whether she fell into that group of mothers showing a depressed T. G. T. This was found to be normal, and she manifested no bleeding tendencies.

Of the three male siblings, one revealed an AA hemoglobin and a P. T. C. deficiency, which is a sex linked defect; the second revealed an SS hemoglobin, which was an autosomal defect, and no coagulation defect. The third and most interesting revealed an AS trait hemoglobin and a severe P. T. C. deficiency. The child had inherited both the sex-linked and the autosomal defects.

The AS trait hemoglobin alone has been found to be the cause of severe hematuria, in some cases requiring surgery as a life-saving measure. The P. T. C. deficiency alone has produced severe bleeding. The combination of the two defects in a single individual would therefore be of serious morbidity prognosis.

55. Congenital Deficiency of Factor VII Complicated by the Coagulation Defects of the Newborn Period. S. FREDERICK RABINER, M.D.*; MYRON WINICK, M.D.,* and CARL H. SMITH, M.D. Department of Pediatrics, The New York Hospital-Cornell Medical Center, New York.

The coagulation disorder occurring most frequently during the first few days of life

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is referred to as hemorrhagic disease of the newborn. This condition is characterized by multiple abnormalities in both the first and second phase of blood coagulation. It is an accentuation of coagulation defects present in the majority of newborn infants and will frequently respond to vitamin K therapy. These defects may interfere with establishing the diagnosis of a coexisting congenital coagulation abnormality. As the infant matures this problem ceases to exist. However, in severe cases, it is important to establish the exact diagnosis immediately since congenital defects do not respond to vitamin K therapy.

A case of severe neonatal hemorrhage due to a congenital Factor VII deficiency is presented in which the diagnosis was obscured by coagulation defects present in the newborn period. Initial studies soon after birth revealed anticipated abnormalities of the first and second phase of coagulation. A congenital defect was suspected because of consanguinity, and the prothrombin time was longer than is found in the usual case of hemorrhagic disease of the newborn.

Serial coagulation studies revealed a gradual improvement of the first phase abnormality, as demonstrated by the thromboplastin generation test, but very little change in the prothrombin time. Correction studies with plasma from patients with known abnormalities showed a pure Factor VII deficiency. There were no abnormalities demonstrable in either parent.

These data indicate the importance of replacement therapy in selected cases of hemorrhagic states occurring in the newborn period. Since the administration of serum or plasma will correct the defects in both the hemorrhagic disease of the newborn and most congenital abnormalities these measures are recommended for patients with severe bleeding when a prompt response to vitamin K does not occur.

56. Serological Conflict Between Mother and Fetus. BELA SCHICK, M.D., and STEPHEN KOVEITY, M.D.* Department of Pediatrics and Laboratory of Microbiology, Mount Sinai Hospital, New York.

In his acceptance speech of the Howland Award, Schick discussed among other problems, the theory that the initiation of the delivery of a baby may be due to an allergic sensitization of the uterus. The serum protein of the fetus is different from that of the mother and acts as an antigen. By interaction of this antigen with sessile antibodies in the uterus, contractions of the uterus are created. The Schultz-Dale test is a classical method for proving the existence of such a specific protein. In the original Schultz-Dale test a virgin uterus of a guinea pig was sensitized by an injection of orchard grass protein digest. By adding a small amount of this protein to the suspension fluid, contractions of the uterus horn are produced. In our experiments the test could be simplified by using pregnant instead of virgin guinea pigs, assuming that the growing fetus acts automatically as a sensitizing protein. We have been able to demonstrate that among eight guinea pigs, six showed a positive Schultz-Dale test. Navel chord serum was used as fetal protein. We are at present not able to explain why two of the guinea pigs did not react.

The results of our experiments support the theory that fetal protein is different from maternal protein. It is capable of sensitizing the maternal uterus, producing contractions, which may initiate the termination of pregnancy at the normal time. We must perform an analogous experiment in the human being. If these experiments would give a positive result, we could extend our theory to explain the normal termination of pregnancy in human beings. Then the way would be open for the study of how to prevent the premature termination of pregnancy.

The application of antiallergic procedures would be the logical approach. This approach was successfully tried by Hirsfield in the prevention of habitual abortion.

* By invitation.

57. Erythroblastosis Fetalis: Attempts at Prevention by Desensitization. FRED H. ALLEN JR., M.D.,* and LOUIS K. DIAMOND, M.D. The Children's Medical Center, Boston.

East, in 1949, described a case in which an Rh-negative woman, whose previous baby was stillborn because of Rh antibodies, was given many intravenous and intramuscular injections of the husband's blood in an attempt at desensitization. The antibody titer rose very high, and then fell to moderate levels. She became pregnant, and the baby at birth appeared normal and survived with small transfusions. Although it was known that a lightly affected baby could follow an erythroblastotic stillbirth, even when the titer was high, East's case was sufficiently remarkable to make others want to repeat the experiment.

In 1954, we began with a patient already pregnant, who had had two previous erythroblastotic stillbirths, and gave her twice-weekly intravenous injections of Rh-positive blood. At 35 weeks a hydropic baby was delivered by section. In 1955, we continued the trial with two other women, neither pregnant at the time, and gave weekly injections over periods exceeding a year. One of these gave birth to a normal Rh-negative baby. The other, more than three years after the beginning of the injections, had an hydropic infant. A fourth woman, in 1956, was started on injections 15 weeks before the onset of pregnancy, injections being continued weekly for 46 weeks. The pregnancy resulted in intrauterine death with hydrops at 32 weeks' gestation.

In all cases the Rh antibody rose and then fell, as it had done in East's case. In no case was the husband's blood used. No more than 5 cc. of blood was administered at one injection (East had given as much as 50 cc.). No untoward reactions to the injections were observed. In two of the four cases anti-Jk^a developed as a result of the injections, and in one of these anti-G (anti-Rh^G) was produced as well. Although the three cases in which Rh-positive fetuses were carried must be classified as failures from the therapeutic viewpoint, much was learned about immunization to blood-group factors. It was a mistake to have taken into the study a woman whose husband was heterozygous for Rh. Although the child turned out to be normal, it might have had erythroblastosis due to other antibodies that developed during the immunization. Further work along the line of these experiments might be rewarding.

* By invitation.

58. Familial Pulmonary Fibrosis and Its Relationship with the Hamman-Rich Syndrome. BERNARD LASKI, M.D., F.R.C.P. (C)*; W. L. DONOHUE, M.D.*; IRENE UCHIDA, Ph.D.,* and J. D. MUNN, M.D.* The Hospital for Sick Children, Toronto, Canada. Introduced by Dr. A. L. Chute.

In 1944 Hamman and Rich published four cases of acute diffuse fibrosis of the lung. These cases were in adults. Since then additional cases of idiopathic fibrosing interstitial pneumonitis have been published. Clinically these patients present a progressive pulmonary insufficiency characterized by increasing dyspnea and cyanosis, associated with progressive changes in the x-ray.

Pathologically the lungs show a characteristic cirrhotic appearance with multiple cystic areas, associated with extensive interstitial fibrosis. Frequently there is a hyperplasia or metaplasia of bronchial and alveolar epithelium.

The cause of this lesion is unknown, and many possibilities have been suggested. Among these are infection, allergy, unknown chemical irritants, collagen disease, and rheumatoid arthritis.

There have been 87 acceptable cases described in the literature, and among these 12 were in sibs. This would appear to be a high incidence for so uncommon a disease. Six cases have been described in children, the first being in 1956.

Our interest in this disease was stimulated by its fatal occurrence in two siblings,

both under one year of age, and by the death of the father from the same disease within one month of the death of the second child. Further careful investigation revealed seven members in all of this family to have been affected. In addition, another family with two affected members has also been found by us.

Clinically our two patients both presented at three months of age with the symptom of "failure to thrive." Despite exhaustive investigation nothing was found, and they both reappeared a few months later with signs of progressive pulmonary disease and died. The father was found to have pulmonary fibrosis and he, too, died of a superimposed acute pneumonia.

Pathologically they all showed the lesions typical of the Hamman-Rich syndrome, and it would seem that one cause at least of this syndrome is on a genetically determined basis.

The family pedigrees, clinical course, and pathological findings will be discussed.

59. Hypoproteinemia and Edema as Early Manifestations of Fibrocystic Disease of the Pancreas. DANIEL S. FLEISHER, M.D.*; ANGELO M. DIGEORGE, M.D.*, and NANCY N. HUANG, M.D.* St. Christopher's Hospital for Children, Department of Pediatrics, Temple University School of Medicine, Philadelphia. Introduced by James B. Arey.

Inadequate intake of protein or renal disease accounts for the majority of instances of hypoproteinemia and edema in infancy. In other infants, inadequate gastrointestinal absorption is often considered but is rarely established as the etiologic factor. Reports of fibrocystic disease of the pancreas and of exocrine hypoplasia of the pancreas in association with edema and hypoproteinemia are uncommon.

This report concerns observations made on three infants (ages 8-10 weeks) referred to this hospital within a period of three months because of generalized edema. All were excellent feeders, had voracious appetites, and had large bulky stools. Owing to episodes of diarrhea or "colic" at one month of age, a diagnosis of "milk allergy" was entertained, and in each case the formula was changed to a soy bean milk preparation. This formula was continued until admission to the hospital. Severe hypoproteinemia was present in each patient and none exhibited significant proteinuria. The clinical course was characterized by temporary improvement followed by sudden deterioration and death in each case at 4 months of age. Sweat chloride levels in the two infants tested were abnormally elevated. Postmortem examination confirmed the diagnosis of fibrocystic disease of the pancreas in all three infants.

In one of the infants, substitution of a low-sodium whole cow's milk formula resulted in elevation of the serum proteins and disappearance of the edema. When soy bean milk formula was reintroduced, edema and hypoproteinemia recurred, only to disappear again when an evaporated cow's milk formula was given.

The possible relationship of the soy bean feedings to the development of the syndrome and the importance of the recognition of severe hypoproteinemia as an early manifestation of fibrocystic disease will be discussed. Studies are in progress aimed at a better understanding of the pathogenesis of the symptom complex.

60. Hirsutism in Adolescent Girls—Possible Stein-Leventhal Syndrome: Report of Three Cases. ALVIN B. HAYLES, M.D.*; MARILYN L. COWGER, M.D.*; ROBERT A. SALASSA, M.D.*; JOSEPH HYDE PRATT, M.D.,* and MALCOLM B. DOCKERTY, M.D.* Mayo Clinic and Mayo Foundation, Rochester, Minn. Introduced by Roger L. J. Kennedy.

An unusual clinical picture consisting of hirsutism, obesity, mild enlargement of the clitoris, and menstrual disturbance was observed in three adolescent girls aged 13, 13, and 14 years. The urinary excretion of 17-ketosteroids, corticosteroids, and pregnanetriol was normal in each patient, and in two

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instances the changes in these urinary steroids following administration of corticotropin and dexamethasone were also normal. Abdominal exploration in each instance revealed the presence of large polycystic ovaries characteristic of those described in patients with Stein-Leventhal syndrome.

It is the purpose of this presentation to relate observations made on these patients and to discuss the Stein-Leventhal syndrome as a possible cause of virilization of the adolescent girl.

61. Syndrome of Congenital Asymmetry (Hemihypertrophy), Shortness of Stature, and Elevated Gonadotropins. HENRY K. SILVER, M.D. Department of Pediatrics, University of Colorado School of Medicine, Denver.

In 1953 we first described the "Syndrome of Congenital Hemihypertrophy, Shortness of Stature, and Elevated Urinary Gonadotropins" in two children, a girl aged 5½ years and a boy 6 years old. Since then I have had the opportunity of studying three additional children with this syndrome.

A review of these patients reveals that in addition to the asymmetry and elevated urinary gonadotropins, certain other characteristics were present in two or more of the children. These include shortness of stature (in 80%), an abnormally low birth weight despite being born at or beyond full term (in 80%), difficulties in pregnancy (in 80%), the presence of cafe-au-lait areas of the skin (in 80%), shortening and in-curving of the little fingers (in 60%), retardation of epiphyseal development (in 60%), a difference in epiphyseal development on the two sides of the body (in two of four patients), and a peculiar inverted "V" shape of the mouth (in 40%).

Photographs of the characteristic findings will be presented, and the possible mechanism producing the syndrome will be discussed.

62. Cortisol Metabolism in the Newborn. ROBERT A. ULSTROM, M.D.* and ELEANOR COLLE, M.D.* Department of Pediatrics, University of Minnesota, Minneapolis. Introduced by John A. Anderson.

At birth plasma levels of cortisol appear to be related to those of the mother. The infant's plasma also contains cortisone, which may also be maternally derived. Studies of pooled plasma by an in vitro method of isotope dilution have shown that cortisol concentration rises during the first 12 hours of extra uterine life, and subsequently declines to levels that are below those of cord plasma during the next three days.

Small amounts, only, of cortisol are excreted in the urine. The unconjugated urinary Porter-Silber chromagens, however, average 21% of the total extractable by methylene chloride. Additional extraction with ethyl acetate is necessary to effect more complete recovery of the very polar steroids present in the free fraction. These very polar steroids, therefore, are the major components of the unconjugated fraction, and studies using labeled cortisol indicate they are metabolites of cortisol. Chromatographic and spectrophotometric techniques have enabled us to tentatively identify 6-beta-hydroxycortisol as the greatest contributor to this fraction. These studies suggest that the failure to find 90% of the corticosteroids conjugated with glucuronic acid (as in normal adults) is at least in part due to the excretion of unconjugatable metabolites. (Reductions of ring A and carbon 3 are necessary preliminary steps to conjugation with glucuronic acid). The additional finding in our laboratory that omission of β-glucuronidase from the usual procedure for hydrolysis of glucuronide conjugates does not greatly change the yield of "conjugated steroid" in urine of newborn infants, causes uncertainty regarding the assessment of the infant's conjugating ability by this method.

* By invitation.

Studies of 51 normal infants show that average total daily steroid (PS chromagen) excretion rises from 0.137 mg. to 0.446 mg. from the first to the seventh day of life. Although the range was great for the group (0.015-0.713 mg/day) few infants approached the normal adult range after correction was made for body surface area. Unlike the plasma pool levels of cortisol, the average urinary excretion values rise progressively.

Cortisol metabolites were also found in bile, and in small quantity in feces. As in adult man, these routes of excretion seem quantitatively unimportant. A more obvious route of excretion not considered above is a fraction of the urinary steroid which is not extracted by the usual procedures. Further extraction of residues with butanol after the above described procedures results in recovery of an additional 20% to 30% of steroids. In addition, the use of C^{14}-labeled cortisol indicates that the Porter-Silber reaction fails to detect approximately 25% of steroids extracted, probably those having undergone side-chain modification. It is probable that the pathways of cortisol metabolism in the newborn are the same as those known to be present in the adult, but that a significant difference exists in the rates at which cortisol enters the various metabolic routes.

63. Sexual Precocity and Pseudoprecocity in Girls. WALTER R. EBERLEIN, M.D.,* ALFRED M. BONGIOVANNI, M.D., and IRIS T. JONES, M.D.* The Childrens Hospital of Philadelphia.

During a four-year period 50 girls with sexual precocity were seen in the Endocrine Clinic of the Children's Hospital of Philadelphia. During the same period 25 girls were seen because of premature breast development (precocious thelarche) and 11 because of premature appearance of pubic hair (precocious pubarche).

In 42 of the 50 girls with sexual precocity no evident cause could be detected. In one case the precocity may have been related to previous therapeutic irradiation of the face. In four patients sexual precocity was associated with the McCune-Albright syndrome (typical skin pigmentation in all four, but bone lesions in only three). Two patients were found to have a granulosa-cell tumor of the ovary. A large, hemorrhagic luteal cyst was discovered at laparotomy in one case.

Although 25 patients appeared to have only precocious thelarche at first examination, 2 subsequently developed sexual precocity and 3 "early adolescence" during the short follow-up period. Similarly 4 of the 11 patients initially diagnosed as precocious pubarche later developed true sexual precocity, and 2 "early adolescence." This case material emphasizes the difficulty in the differential diagnosis of true sexual precocity from normal variations in adolescent development.

The three patients with ovarian tumors will be discussed in detail because of the reputed rarity and diagnostic features of such tumors as a cause of pseudoprecocity in the female. In neither of the two cases of granulosa-cell tumor did the excretion of estrogens significantly exceed the amount found in the urine of normal adolescent girls, and in one an increased excretion of gonadotropins was detected—both of which findings contrast with the usual textbook descriptions of this disease.

64. Congenital Cretinism Associated with I^{131} Therapy of the Mother. ESTEN W. RAY, M.D.*; KENNETH STERLING, M.D.,* and LYTT I. GARDNER, M.D. The Department of Pediatrics, State University of New York, Upstate Medical Center, Syracuse, N. Y.; the Department of Internal Medicine, New York State Psychiatric Institute, and the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York.

The mother of the child to be described is a single woman who developed amenorrhea, hot flashes, and palpitations at 42 years of age. Her thyroid was diffusely

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enlarged, and she had a lid lag. Her serum PBI was 8.1μg. %. Her I^{131} uptake was 35% after 6 hours, 53% after 24 hours. A diagnosis of thyrotoxicosis in a menopausal woman was made, and she was treated with 14.5 mc. of I^{131} five months after her last menstrual period. Only later was it found that she was gravid. Her pregnancy was otherwise uneventful, and a full-term male infant was delivered by Cesarean section six months after the I^{131} therapy. The infant had a yellow discoloration of his skin and an umbilical hernia; otherwise his physical findings were normal.

The infant's neonatal period was uneventful, but his subsequent course was marked by persistent constipation and frequent respiratory infections. His first eight months of development appeared to be normal. Because he did not walk at the age of 19 months a roentgenogram was taken that showed absence of the femoral head epiphyses bilaterally. The child was lethargic but did not show classic cretin facies. His temperature was 97 F, "length age" was 11 months, and "weight age" was 18 months. Testing by the Cattell Infant Intelligence Scale revealed a low normal score. His skeletal maturation did not exceed 3 months. Serum PBI was 1.8μg. %. The child was started on 15μg. of triiodothyronine daily; 15 mg. of desiccated thyroid daily was added after three days. The triiodothyronine was discontinued after seven days, at which time the desiccated thyroid therapy was increased to 30 mg. daily. Two months after the start of therapy the thyroid had been raised by increments to 120 mg. daily. The child's umbilical hernia and yellow skin discoloration cleared. Two months later his height and skeletal maturation had increased, and his serum PBI concentration was in the normal range.

Animal studies indicate that the fetal thyroid is at least three times as radiosensitive as the maternal thyroid. Athyroidism has also been noted in offspring of animals given I^{131} during their pregnancies. Other results indicate that the human fetal thyroid has the ability to accumulate tracer doses of I^{131} by the 12th week of gestation.

It would appear that the present case represents the third reported instance of congenital hypothyroidism associated with I^{131} therapy of the mother. In view of the relative rarity of fertile women who receive therapeutic doses of I^{131} and also in view of the low incidence of sporadic cretinism, a causal relationship between these events in these cases seems a strong possibility. This emphasizes a hazard inherent in the use of I^{131} therapy for women.

65. The Weltmann Reaction as a Screening Test for Detecting Abnormalities in Serum Proteins. SUSAN C. DEES, M.D., and JEROME A. GRUNT, PH.D., M.D.* Department of Pediatrics, Duke University Medical Center, Durham, N. C.

Recent studies of serum protein changes in various disease states have prompted a renewed interest in screening methods for the detection of abnormal sera, even though precise electrophoretic analysis is an increasingly available technique. This has led us to revive our interest in the Weltmann reaction, which enjoyed a vogue in the 30's as a nonspecific qualitative test for changes in serum proteins.

The test consists of heat coagulation of a 1:50 dilution of serum in the presence of dilutions of $CaCl_2 \cdot 6H_2O$ ranging from 0.1% to 0.01%, a so-called coagulation band of 1-10. The factors which alter sera in various diseases result in Weltmann reactions, which range from very low values in acute inflammatory processes to very high values in fibrotic processes, liver damage, prematurity, and in the neonatal period. Normal, healthy individuals have a constant Weltmann value, regardless of age, sex, and various physiologic states.

The sera from 150 patients have been studied by paper electrophoresis, and the results of these analyses correlated with changes in the Weltmann reaction. The

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sera characterized by high β- and γ-globulin produced high Weltmann values. Those with high α-globulins were associated with low Weltmann values.

This correlation between the proportion of the various globulins and the concentration of electrolyte at which the serum is irreversibly coagulated by heat makes the Weltmann reaction a very useful screening test for changes in serum proteins, since its speed and simplicity allows it to be done in any clinical laboratory.

Sera with Weltmann values which are much above or below the normal value of 6, warrant precise electrophoretic analysis. A familiarity with the groups of diseases in which the Weltmann reaction is abnormal may be helpful in pointing toward certain conditions in obscure diagnostic problems. Because there is a close parallel between the Weltmann values and clinical condition in rheumatic fever and tuberculosis, the test is useful in following the progress of such patients. Other examples of the application of the test are in the study of liver function, infectious diseases, and in premature and normal newborns.

66. The Significance of Serum Complement Levels for the Diagnosis and Prognosis of Acute and Subacute Glomerulonephritis. KURT LANGE, M.D.*; EDWARD WASSERMAN, M.D.,* and LAWRENCE B. SLOBODY, M.D. Departments of Medicine and Pediatrics, New York Medical College—Metropolitan Medical Center, New York.

Three thousand fifty-one patients with various renal lesions were examined for serum complement (C′) levels during the past nine years. Two hundred ninety-one cases had the signs and symptoms of acute glomerulonephritis; sixty-one cases presented with a syndrome characteristic of nephrosis, and forty-three cases appeared clinically to have disseminated lupus erythematosus.

All cases of acute glomerulonephritis, except one, had markedly lowered C′ levels. Clinical healing, as evidenced by the disappearance of signs and symptoms of the disease and the return of C′ to normal levels occurred almost simultaneously. While very low C′ levels do not preclude complete healing, such levels tend to be associated with a more prolonged and stormy course, and the prognosis should be guarded.

Persistence of the disease in a subacute stage associated with continued low C′ levels for long periods of time usually indicate a rapid progression of the disease towards renal insufficiency and uremia. Persistent mild proteinuria and the presence of occasional hyaline and granular casts in the urine associated with a return of the C′ levels to normal is usually associated with either a very slowly progressing disease or one in which healing with defect has occurred.

Acute glomerulonephritis in the presence of normal C′ levels occurs only rarely in our experience. Several examples will be demonstrated where the initial, apparently well-founded clinical diagnosis of acute glomerulonephritis was reviewed on the basis of a normal C′ level and further investigation revealed other causes for the hematuria.

In patients with acute glomerulonephritis who develop uremia, C′ levels usually rise to normal owing to the marked reduction of blood flow over the greatly reduced glomerular surface. The remaining available antigenic surface is insufficient to result in a general reduction of circulating C′ level. Similarly, in the experimentally produced disease, C′ levels do not fall if 60%-75% of the animal's kidney tissue has been removed surgically, while in an animal with intact kidneys C′ level falls precipitously with the onset of disease.

All cases of disseminated lupus erythematosus had a marked lowering of C′. Twenty-six per cent of these cases, however, had anticomplementary sera.

It is suggested that C′ determinations would be an important aid in the diagnosis and prognosis of glomerulonephritis.

* By invitation.

67. Experimental Studies in Age-Conditioned Tolerance to Nephrotoxic Serum. PHILIP L. CALCAGNO, M.D.*; PHATICK K. MUKHERJI, M.D.*; MITCHELL I. RUBIN, M.D., and KORNEL L. TERPLAN, M.D.* Department of Pediatrics, University of Buffalo School of Medicine and the Children's Hospital, Buffalo.

In the nephrotic syndrome in children, age seems to be a conditioning factor. No published data exist with regard to the question of age as a possible conditioning factor in modifying the clinical, biochemical, or pathologic expression of the experimental disease.

Nephrotoxic serum was administered intravenously to newborn rats (0 to 3 hours old) using a dosage comparable, on a body-weight basis, to that which produces nephritis in the mature rat (1.4 cc/100 gm. of rat). Urine was studied for its protein content, and plasma levels of cholesterol, albumin, and globulin were determined before the animals were sacrificed. The kidneys were studied by light microscopy using H and E and PAS stains at 1 week, 2 weeks, 3 weeks and 4 weeks of age. Control rats similarly studied were saline injected. These young rats failed to demonstrate clinical, biochemical or pathologic evidences of disease as seen in the mature rat. This was also true when the dosage of nephrotoxic serum was doubled.

A second group of young rats was injected at 2 weeks of age without demonstrating clinical, biochemical, or classical pathologic evidences of nephritis.

Another group of newborn rats was given twice the amount of nephrotoxic serum and later challenged at 2, 3, 4, and 6 weeks of age with a second dose of nephrotoxic serum. None of the rats under 4 weeks of age developed classical clinical, biochemical, or pathologic evidences of disease, which was seen in the 6-week-old rats. By fluorescent techniques it was demonstrated that antibodies were attached to the glomeruli (antigen) on the first day as well as at 2 weeks, 4 weeks, and 6 weeks after the intravenous administration of nephrotoxic serum in the newborn period (0 to 3 hours). When normal rabbit serum was injected into newborn rats, no such fluorescence was observed.

These experiments on some 300 young rats indicate that (1) nephrotoxic antibody is attached to the kidney (antigen) in the newborn rat as early as 0 to 3 hours after birth; (2) young rats fail to demonstrate clinical, biochemical or pathologic evidences of disease as seen in the mature rat.

The factors responsible for this age-conditioned tolerance to nephrotoxic serum are under investigation.

68. Experiences with Amphotericin B in Treatment of Histoplasmosis and Moniliasis. HENRY G. CRAMBLETT, M.D.*; HUGH MOFFET, M.D.,* and SAMIR NAJJAR, M.D.* Department of Pediatrics, University Hospital, State University of Iowa, Iowa City. Introduced by Wallace W. McCrory.

The therapeutic efficacy of amphotericin B given intravenously in therapy of fungal diseases of children is unproved and the potential toxicity of the drug is not fully known. We have employed this agent successfully in treatment of two children with disseminated histoplasmosis and a child with monilial infection which was recalcitrant to other means of therapy.

The first patient, a 4-month-old infant, had disseminated histoplasmosis with hepatosplenomegaly, anemia, thrombocytopenia, and fever. Examination of the bone marrow revealed typical Histoplasma capsulatum, and cultures of blood and bone marrow yielded growth of this organism. Amphotericin B, 151 mg., was administered in 23 intravenous infusions during a period of 35 days with gradual clinical improvement. Serial examinations of bone marrow were performed. At the end of two weeks of therapy there was no evidence of the presence of Histoplasma capsulatum either by culture or examination of the smear.

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There were no evidences of renal toxicity. On two occasions there was moderate fever and on three occasions, episodes of restlessness stiffening of the extremities, grunting respirations, and cutis anserina after administration of the drug.

The second patient, a 4-year-old girl, with disseminated histoplasmosis was also successfully treated. She presented with fever, anemia, hepatosplenomegaly, and thrombocytopenia. Cultures of blood and bone marrow yielded growth of Histoplasma capsulatum. A total of 382 mg. of amphotericin B was administered during a period of 42 days by means of 32 intravenous infusions. Fever as high as 38.3 C (101.9 F) was noted on three occasions in relation to administration of the drug. The concentration of urea nitrogen in the blood was elevated on five occasions but became normal when administration of amphotericin B was temporarily discontinued. Hyaline casts were noted in only one specimen of urine.

The third patient was a 7-year-old child with moniliasis of three years' duration. It was recalcitrant to all means of therapy. The patient had severe involvement of the oral cavity, lips, and nails. A younger sibling with chronic moniliasis had died of adrenal insufficiency. The patient was given a total of 645 mg. of amphotericin B by 22 intravenous infusions during a period of 34 days. During the therapy, cultures became negative for Candida albicans and have remained so. Transient renal toxicity was observed during the course of therapy. This was manifested by rise in concentration of urea nitrogen in the blood and appearance of hyaline casts in the urine. Despite clearing of the moniliasis, adrenal insufficiency developed.

69. Connective Tissue Studies in Rat Nephrosis: I. S^{35} Uptake. JAMES N. ETTELDORF, M.D.; C. M. JOHNSON, M.D.*; GEORGE BROWN, M.D.*; J. R. TEABEAUT, M.D.*; MICHAEL J. SWEENEY, M.D.,* and C. B. FERRELL, M.A.*

In an effort to further elucidate changes in the mucopolysaccharide component of connective tissue in renal parenchymal disease, S^{35} uptake has been studied in experimental rat nephrosis induced by nephrotoxic rabbit serum (NTS).

Increasing doses of NTS (0.5, 0.75, 1.0 ml/100 gm. body wt.) intravenously in divided doses on two consecutive days resulted in increasing severity of disease. S^{35} was administered intraperitoneally in doses of 0.25, 0.5, and 1.0 mc/gm. body wt/day $\times$ 5 as buffered sodium sulfate. The animals were killed on the seventh day, and the S^{35} uptake was determined in the trichloroacetic acid precipitable fraction of the kidney and related to kidney nitrogen content. The Table shows the results. The data have been arranged so as to emphasize sulfate uptake. (NRS=normal rabbit serum.)

Increasing dosage of S^{35} in control animals receiving normal rabbit serum and/or S^{35} resulted in significant increases in S^{35} up-

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S^{35} Uptake in Rate Nephrosis

Rats/Kidney	Cts/Mg. N/Min. Mean	S. D.	S^{35} Dose (Mc/Gm.)	NRS (Ml/100 Gm.)	NTS Dose (Ml/100 Gm.)	Severity of Nephrosis
10/15	47	±15	0.25	0	0	0
4/4	65	± 5	0.5	0	0	0
4/4	68	±18	0.5	0.5	0	0
4/4	89	±19	0.25	0	0.5	Mild
6/12	99	±19	0.25	0	0.75	Moderate
4/4	115	±25	1.0	0	0	0
4/4	137	±18	1.0	1.0	0	0
8/16	127	±44	0.25	0	1.0	Severe
4/4	135	±17	0.5	0	1.0	Severe
4/4	151	± 9	1.0	0	1.0	Severe

take (p=0.05 or greater). Animals receiving 0.5 and 0.75 ml. NTS/100 gm. and 0.25 mc/gm. S^{35} had comparable uptakes; uptakes which were comparable to control animals received 0.5 mc. S^{35}, but uptakes that were significantly greater than control animals received 0.25 mc. Animals rendered severely nephrotic had comparable S^{35} uptakes despite fourfold differences in S^{35} dosages. Finally control animals receiving 1.0 mc. S^{35} had uptakes comparable to the severely nephrotic animals.

The lack of difference in S^{35} uptake in the rats receiving 1.0 ml. NTS, but fourfold differences in S^{35} dosage, suggests the possibility that (1) rat nephrosis results in an increased rate of sulfate turnover in the mucopolysaccharides of the kidneys; (2) the increased rate of turnover occurs early in the disease, and (3) maximum rate of turnover was occurring at the time the animal was killed.

The contrasting progressive increase in S^{35} uptake in control animals receiving increasing doses of S^{35} suggests that the rate of sulfate turnover in the mucopolysaccharides of the kidney of normal rats is slower than that of nephrotic rats. Finally, the similarity in S^{35} uptake between the rats receiving 1.0 ml. NTS, but fourfold differences in S^{35} dosage and the control animals receiving 1.0 mc. S^{35} suggests the presence of a similar amount of exchangeable sulfate in the mucopolysaccharides of the kidneys of both the nephrotic and normal rats.

Because of the diffuse paths of the S^{35} emitted β-rays, radioautographs were impossible to interpret with any degree of quantitative accuracy. In the nephrotic animals no correlation existed between S^{35} uptake and the amount of microscopic amorphous eosinophilic material ("fibrinoid") seen.

70. Connective Tissue Studies in Rat Nephrosis: II. Basement Membrane Metachromasia. J. Robert Teabeaut II, M.D.*; James N. Etteldorf, M.D.; C. M. Johnson, M.D.*; M. J. Sweeney, M.D.,* and Carl B. Ferrell, M.A.*

*By invitation.

Division of Pathology and Microbiology, and Division of Pediatrics, University of Tennessee, Memphis, Tenn.

Kidneys of rats made nephrotic by intravenously injected nephrotoxic rabbit serum and studied for S^{35} uptake were appropriately fixed and examined microscopically. A variety of staining techniques, including H and E, Masson trichrome, Alcian blue-periodic acid-Schiff, Alcian blue-Feulgen, Gridley reticulum, Scharlach R, and Lison for metachromasia were used. Renal lesions characteristic of nephrotoxic serum nephritis were observed. These included exudative and proliferative changes in glomeruli of varying severity dependent upon the amount of nephrotoxic serum given (0.5, 0.75, 1.0 ml/100 gm.). Metachromasia was demonstrated in glomerular basement membranes of 92% of 24 rats that received 0.5-1.0 ml/100 gm. nephrotoxic serum plus 0.25-1.0 mc. S^{35}/gm/day $\times$ 5; the animals that did not show metachromasia were in the group that received 0.5 ml. doses of nephrotoxic serum and showed minimal nephrotic changes histologically. Animals that were made severely nephrotic by 1.0 ml. doses of nephrotoxic serum had high S^{35} uptakes and demonstrated metachromasia even though the dose of S^{35} varied from 0.25-1.0 mc/gm. Similarly severely nephrotoxic animals receiving 1.0 ml/100 gm. NTS but no S^{35} demonstrated metachromasia. Control animals that received either S^{35} alone, normal rabbit serum alone, normal rabbit serum plus S^{35}, or small amounts of nephrotoxic serum alone did not show metachromasia.

Since metachromasia depends on polymerization of the substrate to induce polymerization in the dye, these findings indicate that nephrotoxic rabbit serum nephritis in the rat is accompanied by increased polymerization of sulfur containing mucopolysaccharides in the glomerular basement membranes.

71. Antibiotics in the Treatment of β-Hemolytic Streptococcal Pharyngitis: Factors Influencing the Results. MAXWELL STILLERMAN, M.D.,* and STANLEY H. BERNSTEIN, M.D.* Long Island Jewish Hospital, New Hyde Park, N. Y. Introduced by Samuel Karelitz.

The effectiveness of penicillin V, penicillin V potassium, benzathine penicillin G, erythromycin, and tetracycline in eradicating β-hemolytic streptococci from the pharynx of 410 infected patients or carriers was studied from April, 1956, to June, 1958. Penicillin V and penicillin V potassium were administered in daily oral doses of 375 and 750 mg. (600,000 and 1,200,000 units) for 10 days, the benzathine penicillin G once intramuscularly in similar doses, and the broad spectrum antibiotics in daily oral doses of 30 to 50 mg. per kilogram up to 1 gm. for 10 days.

The bacterial cure rate was 84% for 224 patients treated with penicillin V and penicillin V potassium, and 86% for 129 patients treated with benzathine penicillin G in combined doses. Of 23 patients treated with erythromycin, 48%, and of 34 patients treated with tetracycline, 38% were cured.

The majority of the clinical bacterial relapses developed 14 to 28 days after the onset of penicillin V orally and 24 to 32 days after benzathine penicillin B, 375 mg. intramuscularly. Approximately half of the patients with bacterial relapses had clinical manifestations of pharyngitis.

Factors which might be responsible for the development of relapses and failures were investigated. In the host, the possibility of local factors at the site of infection was suggested by the significantly lower cure rate of 57% among 52 relapses and failures re-treated with the penicillin preparations compared with the curte rate of 85% among the 353 cases treated initially with this antibiotic. When early infections were cured, type-specific antibodies were not found in the convalescent sera of 10 cases tested, and the rise of antistreptolysin-O, antihyaluronidase, and antistreptokinase was inhibited in 83% of 85 cases. Household contacts harbored streptococci of the same group and type as the patient in 22% of 204 cases. Antibiotic sensitivity of 25 strains of streptococci isolated prior to and following relapses revealed no emergence of resistant strains to penicillin and erythromycin. Four Group A nontypable strains were resistant to tetracycline.

Complications consisted of one case of otitis media and one case of glomerulonephritis developing 12 and 22 days respectively after the onset of treatment. No case of rheumatic fever was observed.

These data indicate that penicillin was definitely more effective than erythromycin and tetracycline in eradicating β-hemolytic streptococci from the host in the doses used. There was no significant difference in the effectiveness of penicillin V, penicillin V potassium, and benzathine penicillin G. Attention is drawn to the relapse and failure rate of 15% in these patients despite penicillin therapy. Possible explanations for the relapses and failures are (*a*) incomplete eradication of the microorganisms; (*b*) inhibition of immunity in cured patients who are subsequently reinfected by household contacts harboring streptococci of the same serologic type; (*c*) tetracycline-resistant hemolytic streptococci, and possibly (*d*) local factors at the site of the infection.

72. The Role of Staphylococci in Newborn Nurseries. KATHERINE SPRUNT, M.D.* Department of Pediatrics, College of Physicians and Surgeons, Columbia University and the Babies Hospital, New York. Introduced by Hattie E. Alexander.

There is general agreement among those who have studied recent outbreaks of severe staphylococcal disease in the newborn and their families that the nursery is the focal point of these epidemics, and that the causative agent is one of a few strains of coagulase-positive hemolytic Staphylococcus

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aureus, most commonly the 80/81 strain. Because of the frequent association of the 80/81 strain with disease, its appearance in a nursery is viewed with alarm and is considered in some quarters adequate reason for closing a nursery or treating all the normal babies with antibiotics. This paper presents data which suggest that staphylococci alone, regardless of phage type, are not responsible for the epidemic incidence of Staphylococcus disease.

During the past year a careful study of the frequency of staphylococcal colonization and staphylococcal disease in babies, during their five-day stay in the Sloane newborn nurseries of the Presbyterian Medical Center and after a six-week follow-up period after discharge, failed to reveal an unusual incidence of Staphylococcus disease. This "normal" interlude has been used to study normal fluctuations of staphylococcal phage types in four nurseries during a year in which the 80/81 organism has appeared from time to time in our own patient population and can also be assumed to be present in the New York City population because of reports of epidemics in other local institutions. Between 75% and 90% of the babies in the four nurseries are regularly found to be colonized with coagulase-positive staphylococci by the time of discharge on the fifth day. The strains of Staphylococcus have varied widely, and it is common for one type to predominate in any one nursery at one time. The predominant strains shift frequently, their predominance generally lasting about two weeks. The 80/81 strain has behaved in like manner, appearing sporadically from time to time, or acting as the predominant strain for approximately two weeks and then disappearing. The data indicate that the presence or predominance of this strain has had no perceptible effect on the colonization rate or staphylococcal disease as determined by cultures and hospital records and by routine follow-up studies six weeks after discharge.

Information derived from a year's experience with varying strains of staphylococci in four normal nurseries suggests that the presence of the 80/81 strain alone is not sufficient to cause disease. Some other factor must be required, a factor as yet unknown, but with the epidemiological characteristics of a virus.

73. Transmission of P^{32}-Labeled Candida Albicans to Newborn Mice at Birth. PHILIP J. KOZINN, M.D.*; CLAIRE L. TASCHDJIAN, B.S.*; JAMES J. BURCHALL, B.S.,* and HARRY WIENER, M.D.* Department of Pediatrics, Maimonides Hospital, Brooklyn. Introduced by Benjamin Kramer.

A high correlation between maternal vaginal and neonatal oral candidiasis indicates that the maternal birth passages serve as a source of infection in newborn infants. However, this pathway of infection has not been proved unequivocally.

It was therefore attempted to induce vaginal candidiasis in gravid mice at term, and to recover Candida albicans from the oral cavity, intestines, and skin of the newborn mice. The strain of C. albicans used for infection of the mothers was labeled with P^{32} by growing the culture on media containing radiophosphate. This method was elaborated as a means of identifying a given pathogen and rendering it distinguishable from other strains of the same species, so as to trace its transmission from one host to the next.

C. albicans was recovered from 70% of the newborn mice within 24 hours after birth. More than 50% of all cultures were isolated from the oral cavity and the gastrointestinal tract. Radioactivity was present in 90% of the cultures obtained, as tested by autoradiographs, and in 67% of the cultures as tested by means of a gas-flow counter.

* By invitation. This paper will appear in full in a forth coming issue of this Journal.

74. Fibrinous Bronchitis: Its Mechanism, Treatment, and Implications. VIVIAN TAPPAN, M.D.* Department of Pediatrics, Yale University School of Medicine, New Haven, Conn. Introduced by Milton J. Senn.

During the past two years at the Yale Medical Centre, two patients aged 13 and 15 years respectively, with pulmonary stenosis and interauricular septal defect, developed fibrinous casts following cardiac surgery. In each instance the preoperative medical and laboratory data were characteristic of a moderately severe degree of pulmonary stenosis in combination with a small but significant right-to-left interatrial shunt, including cardiac catheterizations and angiocardiograms. Both patients gave the story of bruising easily, and ecchymoses had been noted previously. However, preoperative hematologic studies were normal. The histories differ only in a greater incidence of respiratory infections, and of antecedent operations in the older child.

In the younger boy cardiac repair was by open heart valvulotomy, together with the closure of the atrial defect; in the older boy, pulmonary valvulotomy was by the Brock technique. The operating times were eight hours and five and one-half hours respectively. Both patients developed acute respiratory distress postoperatively.

Respiratory distress was severe in the younger patient, requiring tracheotomy eight hours postoperatively. Thereafter assisted respiration, repeated attempts at bronchoscopic aspirations, and the use of I. P. P. B. gave only slight and temporary relief.

Arterial blood chemistries on the second postoperative day revealed a pH of 7.23; a CO_2 of 21.2 mEq/L.; a calculated pCO_2 of 52 mm. Hg, and an N. P. N. of 78; his hematocrit was 47.

Later, on the same day, two small, delicate, fawn-colored bronchial casts were isolated from the aspirated bronchial fluids. Subsequent histochemical and enzymatic studies proved that these casts were almost wholly made up of fibrin. The patient died on the fourth postoperative day.

Immediate respiratory distress was much less severe in the older child, and improved markedly after the third postoperative hour. His subsequent course was essentially uneventful until the seventh postoperative month, when he developed acute fibrinous bronchitis. During the preceding week the patient had increased his physical activity, practically overnight, from a walking level to include running, baseball, and swimming underwater. Studies of his casts by histochemical and enzymatic methods proved them to be chiefly fibrin.

It is suggested that fibrin cast formation is to be traced (1) to the pathologic transudation of plasma fluids and plasma proteins into the peripheral respiratory tract, and (2) to the polymerization of activated fibrinogen under the special conditions created by local respiratory acidosis, and by disturbed intrapulmonary pressures.

The mechanism is believed to be one of acute overloading of anatomically inadequate pulmonary circulation with blood in individuals with limited gas exchange, breathing against acutely imposed obstructions.

Based upon this pathogenic concept, the older boy has been treated for more than two years with beneficial effects by (1) the use of continuous broncholysis, and (2) by alkalization in amounts designed to keep him in a state of mild alkalosis.

However, the patient discontinued medications for varying periods of time when he decided "he was well." Thus, it was possible to compare his clinical course and significant laboratory findings while "on and off" treatment.

These findings will be discussed in relation to the concept and therapeutic approach.

This concept and therapeutic approach are thought to have useful implications in the general area of pathologic conditions of the lungs.

* By invitation.

75. Chemoprophylaxis During Respiratory Infections in a Private Pediatric Practice. EDWARD H. TOWNSEND JR., M.D.* Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Introduced by Gilbert B. Forbes.

The advisability of antibiotic prophylaxis in viral respiratory diseases is a subject of current interest. It was decided to study this problem in cases seen in private practice since other investigations have been concerned primarily with hospitalized patients.

The study was begun on Oct. 1, 1957, and concluded April 30, 1958. Patients were seen in the home or office, and assigned to one of three treatment programs by a random selection method designed by a statistician.

Study was made of 845 cases of viral respiratory illness, occurring during a season when an epidemic of influenza, Type A (Asian strain) was present in the community. Of these, 102 cases proved to be measles and 743 others a less well-defined type characterized primarily by fever, cough, and other respiratory symptoms. Of the 309 patients receiving full therapeutic doses of tetracycline or a sulfonamide, 43 (14%) developed complications, as did 19 (8.4%) of the 233 patients who received prophylactic doses of the same drugs. Of the remainder—303 patients—who were treated symptomatically, 27 (8.9%) developed complications. There is no statistical difference among these three treatment groups.

From the point of view of presenting symptoms and signs, there was no difference among the three treatment groups except when croup, fever, or cough were the presenting symptoms, or when inspiratory rales were present, in which case the symptomatic group showed a statistically significant lower incidence of complications ($P=0.01$).

Division of patients with respect to age, sex, and family size showed no difference among the three treatment programs, nor did the presence within a family group of similar or other (bacterial) illnesses.

The white blood count was of no value in predicting the likelihood of complications.

Patients presenting a history of recurrent respiratory illnesses had a lower incidence of complications ($P=0.05$) when antimicrobial agents were given than did the symptomatic group. This category is the only one favoring chemoprophylaxis.

There was no difference in the duration of illness among the three treatment programs. Most cases were seen in the first three days of illness and, except for measles, signs of recovery were present shortly thereafter. A complication was defined as a new sign or symptom occurring during the illness, excluding persistence of fever. Of the 89 complications pneumonia accounted for 30 cases (34%), 21 of whom had received full therapeutic doses. Otitis media occurred in 39 cases (42.5%), appearing on the third to fifth day of the original respiratory illness with no evident relationship to the day on which therapy was begun. These were equally distributed among the three treatment programs.

Other complications included tonsillitis, cervical adenitis, sinusitis, bronchitis, and nephritis.

76. Follow-Up Studies upon Infants with Coarctation of the Aorta and Patent Ductus Arteriosus. M. R. BEHRER, M.D.*; F. PETERSON, M.D.,* and D. GOLDRING, M.D.* The Washington University School of Medicine, St. Louis. Introduced by A. F. Hartmann Sr.

It has been our feeling that infants born with coarctation of the aorta and an intra- or extracardiac shunt frequently develop congestive failure early in life which is resistant to intensive medical treatment. Surgical correction of the defects is, therefore, indicated as a life-saving procedure.

This is a report upon 10 infants with the above malformations who were operated upon. Eight of these patients sur-

* By invitation.

vived. Of these patients, seven were in congestive heart failure, and one had a history of failure. Seven of the eight had marked systolic hypertension and the blood pressure gradients between the upper and lower extremities varied between 40-130 mm. Hg.

Seven of the patients were 4 months and under at the time of operation and one was 18 months. Seven patients had a patent ductus arteriosus demonstrated at operation in addition to the coarctation.

The survivors have been followed from one to four years postoperatively and have been reevaluated. The following information has been gathered.

1. No hypertension has been demonstrated in any patient.
2. Four patients have normal blood pressure gradients between the upper and lower extremities and four patients have only a 10-20 mm. Hg gradient.
3. Four patients show definite evidence of an intracardiac defect (one patient was shown to have an interventricular septal defect). In the remaining four patients there is no clinical evidence of additional cardiac defects.

We feel that this experience reaffirms our conviction that early surgical intervention in infants with coarctation and additional cardiac defects is feasible and life-saving. There are no indications that the coarctation was reestablished in these patients during this period of follow-up.

77. Congenital Dextrocardia: A Clinical, Roentgenologic, Electrocardiographic, Angiocardiographic, Catheterization, and Autopsy Study of Thirty-Six Cases. RENE A. ARCILLA, M.D.,* and BENJAMIN M. GASUL, M.D.* University of Illinois College of Medicine, Chicago. Introduced by Heyworth N. Sanford.

During the past 12 years, since the establishment of the cardiophysiology department of the Cook County Children's Hospital, 36 cases of congenital dextrocardia were studied. Complete physical examination, including phonocardiography, roentgenologic examination with barium esophagram in the PA and oblique views, and a 15-lead electrocardiogram, were done routinely. Twenty-seven patients had angiocardiography; eight had cardiac catheterization, and twelve came to autopsy. There were 21 males and 15 females, and the ages varied from birth to 8 years.

The literature on this subject is replete with confusing and contradictory opinions regarding the position and anatomy of the cardiac chambers and of the great vessels. We have not encountered in our series or in the literature the so-called mirror-image isolated dextrocardia, that is, Type I dextrocardia without situs inversus. The clinically reported cases of isolated dextrocardia undoubtedly are of the Type II or Type III dextrocardia.

The patients are classified as follows:

Type I. Mirror-image dextrocardia—8 cases
- A. With intracardiac anomaly—5 cases
- B. Without intracardiac anomaly—3 cases

Type II. Dextroversion complex—12 cases
- A. Complete pivotal dextrocardia (with intracardiac anomaly)
- B. Incomplete pivotal dextrocardia (mesoversion)—9 cases
  1. With intracardiac anomaly—none
  2. Without intracardiac anomaly—3 cases

Type III. Mixed dextrocardia—2 cases
- A. Mirror-image atria, pivotal ventricles—1 probable case
- B. Pivotal atria, mirror-image ventricles—1 case

Type IV. Congenital extrinsic dextrocardia (pseudodextrocardia)—14 cases
- A. Simple dextroposition—1 case
- B. Dextroposition with pivotal rotation
  1. With mild pivotal rotation—1 case
  2. With midpivotal rotation—8 cases
  3. With severe pivotal rotation—4 cases

The angiocardiogram and postmortem findings were the basis for this classification. In Type I the venous atrium and ventricle are anterior to the corresponding arterial chambers, as they are in the normal heart, while in Type II the arterial chambers are anterior to the venous chambers. Type III represents a combination of

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Types I and II. In Type IV congenital anomalies of the lungs, left diaphragm, of the spine, or of the chest cage account for the cardiac displacement. In simple dextroposition, the heart is shifted to the right along the frontal plane only. In dextroposition with pivotal rotation, there is an additional rotation along the horizontal plane to the right. The latter probably represents an advanced degree of the displacement, and in one case, where left upper lobectomy was done, the heart reverted to a simple dextroposition and later to a normal position.

The P wave in the bipolar and unipolar limb lead tracings, especially Lead I, aVr, and aVl, is the best electrocardiographic criterion for the differential diagnosis of dextrocardia, since the QRS configuration readily changes with ventricular hypertrophy. In the two cases of dextrocardia Type III, however, the ventricular chamber arrangement was not similar to the atrial. In Type II of the complete type deep Q in Lead I and aVl with negative T waves were present in 70% of cases. Those of the incomplete type did not show this. The Type IV dextrocardia with severe and midpivotal rotation similarly had deep Q in Lead I and aVl, but with upright T waves. Schematic vector loops illustrate this abnormality. The tracings were normal in simple dextroposition.

Aside from outlining the abnormal position of the chambers, the specific angiocardiographic and catheterization findings depended on the intracardiac anomaly present.

Slides illustrating the different types of dextrocardia will be shown.

78. Ventricular Septal Defect: Indications and Contraindications for Surgery. CATHERINE A. NEILL, M.D.,* and HELEN B. TAUSSIG, M.D. Department of Pediatrics, The Johns Hopkins University Harriet Lane Home Cardiac Clinic, The Johns Hopkins Hospital, Baltimore.

Open heart surgery for ventricular septal defect has progressed in the past four years from a hazardous pioneering procedure to a widely practiced operation. The discussion of types of pump, causes of postoperative mortality and morbidity, and other technical matters has tended to obscure the actual indication for surgery. This paper is concerned with three questions: 1. Should all patients with ventricular septal defect undergo surgery? 2. If not, what considerations should govern the physician's recommendation for a specific child? 3. Are there any absolute contraindications to surgery?

The answers vary with the type of ventricular defect and its prognosis and the safety of surgery in the individual institution.

Group I: Maladie de Roger.—Small defect, no cardiomegaly, small or moderate shunt and normal pulmonary resistance; pulmonary artery pressure, 40% or less of systemic; electrocardiogram essentially normal.

These patients have little to gain from surgery and a normal life to lose. Surgery is contraindicated at the present time.

Group II: Ventricular Defect of Moderate Size.—Slight cardiomegaly, mild symptoms of growth retardation and dyspnea; PA pressure 40% to 80% of systemic. Little or no increase in pulmonary resistance. Electrocardiogram with either left ventricular hypertrophy or early to moderate right ventricular hypertrophy.

The ideal age for surgery in these patients is between 3 and 15 years of age. Their natural life expectancy is good; there is no evidence that pulmonary hypertension will develop at puberty. Surgery should therefore be performed only if the operative mortality for this group is under 6%.

Group III: Ventricular Septal Defect, Large.—Moderate to great cardiomegaly, severe retardation of growth and dyspnea; pulmonary resistance moderately elevated;

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pulmonary artery pressure 80% to 100% of systemic. Electrocardiogram shows combined ventricular hypertrophy.

These patients need surgery and will show great benefit if successful. Sometimes surgery in infancy may be life-saving: postponement until between 3 and 15 years of age is usually wiser. The pulmonary pressure will sometimes decrease as the infant or child grows. The operative mortality should not exceed 15% in childhood. In infancy, operation is indicated only if the infant is in serious difficulty.

Group IV: Ventricular Defect with Shunt Reversal (Eisenmenger Type).—Size of defect and size of heart variable, cyanosis intermittent at first, later persistent; pulmonary resistance markedly elevated; PA pressure equal to or higher than systemic; electrocardiogram shows right ventricular hypertrophy with little or no left ventricular hypertrophy.

This is probably the only group where surgery should be performed in infancy, because in this group pulmonary vascular changes are progressive and eventually preclude success. Beyond early childhood and certainly after adolescence the risk is high and surgery is usually contraindicated.

Group V: Ventricular Septal Defect with Complications.—These complications include large patent ductus or another large shunt, endocardial fibroelastosis, aortic incompetence, aortic or mitral hypoplasia, pulmonary stenosis without significant overriding or right-to-left shunt, multiple fenestrated defects in muscular septum, corrected transposition.

In this group, the relative importance of the various complications must be assessed in order to evaluate the amount to be gained from successful closure of the ventricular defect.

In summary, surgery is contraindicated at present in the asymptomatic patient with a small shunt and in those with persistent shunt reversals. In all others, surgery should be recommended only if the defect is large enough to cause difficulty and if risk of operation at the center concerned is low.

79. Ventricular Septal Defect: Prognosis of Congestive Heart Failure in Infancy. BEVERLY MORGAN, M.D.*; SYLVIA P. GRIFFITHS, M.D.,* and SIDNEY BLUMENTHAL, M.D.* Department of Pediatrics, College of Physicians and Surgeons, Columbia University and Babies Hospital, New York. Introduced by Rustin McIntosh.

This study was undertaken to evaluate the prognosis of the patient with a ventricular septal defect who has developed congestive heart failure during infancy. The original concept of Roger in 1879 implied a benign course in patients with this anomaly while some recent observations suggest that these patients rarely survive childhood.

Clinical and pathologic data for a 10-year period (1948-1958) pertaining to 125 patients with an isolated ventricular septal defect have been studied, including 30 cases from the Pediatric Pathology Laboratory and 95 cases from the Pediatric Cardiac Service. Analysis of the clinical course of these 125 patients indicates that the majority did not develop serious symptoms in childhood. Eighteen patients had a history of congestive heart failure in infancy; all of these experienced their initial episode of failure prior to 6 months of age. Ten of these patients died in heart failure in the first year of life while eight are alive and being followed.

The clinical course and laboratory findings of the 18 patients with congestive heart failure did not show significant differences between the survivors and those who succumbed. Of 30 postmortem cases, 25 died in the first year of life. Ten of the infants died of congestive heart failure, three of pulmonary infection, and twelve of severe noncardiac anomalies and/or prematurity. The ventricular septal defect varied between 4 and 15 mm. in diameter in the group succumbing to failure, and of these nine were high defects involving the mem-

* By invitation.

branous portion of the ventricular septum while the tenth was a large muscular defect. In the three patients who died of pulmonary infection, the ventricular septal defect was from 10 to 18 mm. in diameter, despite which heart failure was not a problem. Among the 12 patients in whom the cause of death was prematurity and/or noncardiac anomalies the size of the defect was significantly smaller than in the preceding groups and varied from 1 to 7 mm. The five late deaths followed surgery.

80. Acid-Base Abnormalities Encountered with the Gibbon-Mayo Pump Using Blood Flow Rates of 2-2.4 Liters per Square Meter of Body Surface per Minute. A. F. HARTMANN JR., M.D.*; A. ROOS, M.D.,* and D. GOLDRING, M.D.* The Washington University School of Medicine, St. Louis. Introduced by A. F. Hartmann Sr.

It was noted that the venous blood of postoperative patients who had undergone repair of serious congenital cardiac malformation using the Gibbon-Mayo pump showed profound acidemia, while the arterial oxygen saturation (ear piece oximeter) was well above 90%. Their clinical appearance seemed much worse than the arterial oxygen saturation would indicate.

It was because of these discrepancies that the following studies were undertaken.

1. Thirty patients who had surgical repair of cardiac defects using extra corporeal support were studied. The following blood constituents were determined: pH, CO_2, lactic acid, sodium, potassium, calcium, phosphorous, chloride, oxygen saturation, and total and fractional proteins on the (*a*) donor blood, (*b*) blood in the pump prior to bypass, (*c*) arterial and venous blood of the pump at the end of bypass, (*d*) femoral artery and vein blood of the patient four hours postoperatively.

2. The postoperative A-V difference studies were also carried out on 10 postoperative hypothermia patients and on a similar number of patients who had a unilateral thoracotomy for the repair of a patent ductus arteriosus or coarctation of the aorta.

Differences Between Arterial and Venous Blood in a Typical Case

	Arterial Blood	Venous Blood
pH	7.34	7.22
CO_2	15.9 (whole blood) mEq/L.	20.2 (whole blood) mEq/L.
pCO_2	33 mm. Hg.	54 mm. Hg.
Calculated acid excess	4 mEq/L.	4 mEq/L.
Lactic acid	5.4 mEq/L.	5.8 mEq/L.
Oxygen saturation	91.9%	28%

Conclusions

1. The acidemia of the pump blood before and during bypass was mild and was due to the method of collection and processing of the donor blood. This was primarily due to stasis, glycolysis, and dilution with saline.

2. The A-V difference of the pump blood at the end of bypass was in the normal range, indicating good circulation during bypass.

3. The A-V difference of the patient's blood four hours after bypass was marked, as is shown by findings in a typical case.

Similar studies in the posthypothermia and unilateral thoracotomy patients revealed only moderate changes.

4. These A-V differences indicate poor circulation in the extremity from which these samples were drawn. This could be accounted for by (1) low cardiac output (2) local vasospasm or a combination of both.

Studies are presently in progress to resolve this problem.

81. The Effect on the Child's Heart of Early Resumption of Normal Physical Activity Following Acute Rheumatic Fever as Evaluated Two to Fourteen Years Later. BESSIE L. LENDRUM, M.D.*; ALBERT J. SIMON, M.D.,* and IRVING MACK, M.D.* Herrick House, Bartlett, Ill. Introduced by Julius B. Richmond.

Prolonged bed rest and restriction of physical activity has in the past been con-

* By invitation.

sidered essential in the treatment of patients convalescing from acute rheumatic fever. Well-controlled long-term studies of the effect of prolonged bed rest on the heart would be important as guides to management of acute rheumatic fever, but are lacking. Herrick House, an institution for children convalescing from acute rheumatic fever, was one of the first institutions to abandon prolonged bed rest and adopt accelerated physical rehabilitation of convalescents as soon as signs of the acute rheumatic process had subsided. A long-term follow-up study to assess the effect on the heart was undertaken; 269 children thus managed have been followed from 2 to 14 years. Their cardiac status was compared with that of 91 children who constituted the control group. They were children similarly studied and concurrently followed but had been managed by prolonged bed rest immediately prior to admission to Herrick House.

Variables known to affect cardiac status were analyzed and found to be either comparable or to favor the control group slightly. These included (1) the quality of medical care following discharge from Herrick House; (2) use of antistreptococcal prophylaxis; (3) incidence of recurrences, chronic myocarditis, and subacute bacterial endocarditis; (4) age distribution, and (5) number of years in the study.

The cardiac status was assessed by a simple, but effective, arbitrary scoring system based upon changes in heart size (x-ray), murmurs, and blood pressure alterations compatible with dynamic aortic insufficiency. Of the patients treated by rapid rehabilitation, 26% were found to have evidence of more cardiac damage at their final examination than on initial admission to Herrick House, whereas 41% of the control group subjected to prolonged bed rest were found to have cardiac deterioration, suggesting that early rehabilitation did not adversely affect the heart. This conclusion was essentially unaltered after excluding from both the study group and the control group patients with rheumatic recurrences, chronic myocarditis, and subacute bacterial endocarditis. Of the resulting smaller study group of 170 patients, 12% were found to have deterioration, while in the control group of 52 patients 25% had cardiac deterioration. Thus, comparison of findings in the study group with those in the control group lead to the conclusion that no deleterious effect on the heart appeared to result from rapid physical rehabilitation of children convalescing from acute rheumatic fever. The results rather suggest a beneficial effect, confirming earlier reports of our preliminary observations.

Additional well-controlled, long-term clinical studies are needed to evaluate the effect of physical activity on the ultimate effects of rheumatic myocarditis. The obvious adverse economic, sociologic, and psychological effects of prolonged bed rest make it desirable to abandon the practice of unnecessary restriction of activity, which this study suggests is not necessary and may even be contraindicated for optimal cardiac recovery.

82. **Magnesium Kinetics in Muscular Dystrophy.** LEON HELLMAN, M.D.*; BARNETT ZUMOFF, M.D.*; ABRAM KANOF, M.D.,* and BENJAMIN KRAMER, M.D. The Sloan-Kettering Institute for Cancer Research, the Maimonides Hospital and the Jewish Chronic Disease Hospital, New York.

The nature of metabolic disturbances related to Erb-Duchenne muscular dystrophy is poorly understood. In view of the prominence of magnesium in the intracellular compartment of muscle and its association with many enzyme systems, the possible role of disturbances in magnesium metabolism in muscular dystrophy was investigated. The availability of Mg^{28}, a magnesium isotope with a half-life of 21.5 hours, provided a tool for the investigation of magnesium kinetics in intact human subjects. Three subjects were studied:

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R. G., male, age 10 years; S. V., male, age 13; and G. V., male, age 15. All had typical muscular dystrophy of the Erb-Duchenne type. Each patient received an intravenous dose of approximately 50μc. of Mg^{28}, administered over a 30-minute period, and equivalent to 1.2-1.5 mg/kg. body weight of magnesium as $MgCl_2$. The conditions of administration were standardized to conform with previous studies of normal controls, since the amount of magnesium given was appreciable, and it had been found necessary to standardize the loading factor. The findings were as follows:

1. *Plasma Disappearance Curve.*—In normal subjects, several variable fast components are observed during the first two to three hours after administration, and there is a constant slow component, apparent from three to eight hours, believed to represent the rate of penetration of Mg^{28} into cells. The half-time of this slow component varies between 250 and 350 minutes in normals. In R. G., S. V., and G. V., the slow component half-times were 330, 298, and 298 minutes.

2. *Fecal Excretion.*—Normal subjects excrete less than 1% of the intravenous Mg^{28} into the feces in three days. The three dystrophic children excreted similarly minute amounts of Mg^{28} into the feces.

3. *Erythrocyte Penetration.*—Within an eight-hour period, normal subjects show no detectable penetration of Mg^{28} into erythrocytes. This was also the case for the children with dystrophy.

4. *Cumulative Urinary Excretion.*—Normal subjects excrete 10%-12% of the intravenous dose in the urine within a day. Subject R. G. excreted 5.7%; Subject S. V. excreted 7.5%; Subject G. V. excreted 13.5%.

5. *Estimated Intracellular Accumulation.* This figure is calculated by determining the percentage of radioactivity which has disappeared from the extracellular fluid, but has not been excreted from the body. In normal subjects, this figure is from 74%-76% of the dose. In Subject R. G., it was 83%; in Subject S. V., 90%, and in Subject G. V., 73%.

It is apparent from these data that these measurements of Mg^{28} metabolism are not abnormal in muscular dystrophy. The normal disappearance of magnesium from the extracellular fluid into another, unknown, body compartment suggests either that the diseased muscle is still able to take up magnesium or that magnesium primarily disappears into bone or some tissue other than skeletal muscle.

83. Febrile Seizures: Indications for Continuous Anticonvulsant Therapy and Observations on Prognosis. J. GORDON MILLCHAP, M.D.*; JACK A. MADSEN, M.D.*; and LOUIS M. ALEDORT, B.S.* Department of Pediatrics, Albert Einstein College of Medicine, New York. Introduced by Henry L. Barnett.

The advisability of continuous anticonvulsant therapy in the management of febrile seizures is controversial. Whereas some authors have recommended phenobarbital or diphenylhydantoin to be given after the first seizure and continued until the age of 3 or 4 years, the majority of practitioners are opposed to such therapy and prescribe phenobarbital only at the time of subsequent febrile episodes. Continuous treatment with phenobarbital after the occurrence of a fourth seizure, as advocated by some, would appear to have little prophylactic value, since the chance of further recurrence of febrile seizures is small. Only 12% of 110 patients in the present study had more than four seizures. In order to determine more accurately the indications for continued therapy, patients in this investigation were unselected and were treated alternately by one of two methods. Some patients received phenobarbital (mean daily dose, 3.8 mg/kg.) only at the time of each febrile episode, while others were given regular daily doses of phenobarbital (mean dose, 3.1 mg/kg.) or diphenylhydantoin (mean dose, 10 mg/kg.), in addition. Antipyretic therapy

* By invitation.

was used when indicated. The incidence of recurrence of febrile seizures was compared in the two groups.

Febrile seizures recurred in 53% of 19 patients treated intermittently and in 43% of 21 patients treated continuously with phenobarbital. Thus, the results of continuous therapy were not superior to those of intermittent therapy alone ($P>0.05$); seizure control was poor and of questionable degree in both groups. Febrile seizures recurred in all seven patients given diphenylhydantoin by continuous adminstration. The ineffectiveness of diphenylhydantoin against experimental febrile seizures in animals was reported previously.

In the prophylactic treatment of uncomplicated febrile seizures the long-continued administration of anticonvulsant medication is unwarranted. Such therapy should be reserved for patients in whom seizures occur with minimal elevation of temperature or for those who have suffered a nonfebrile seizure in addition.

One or more nonfebrile seizures had occurred in 18 (17%) of 95 patients who were followed during the period of study between July, 1956, and June, 1958. A history of spontaneous seizures in the family was elicited in 39% of patients in this group compared with 20% of the patients with febrile seizures alone. A family history of febrile seizures was obtained with equal frequency in both groups (30% and 33%). The incidence of abnormal birth in the two groups was 33% and 17%, respectively. The occurrence of spontaneous seizures appeared to be related to a significantly greater hereditary tendency and/or to brain injury acquired before the onset of febrile seizures ($P<0.05$). In laboratory animals subjected to four seizures with hyperthermia at intervals of one or two days, the threshold to nonfebrile seizures, as measured by an electroshock current, was *increased* by 20% when compared with controls ($P<0.05$).

That hyperpyrexia with prolonged convulsions may result in neuronal necrosis and severe brain damage is well known. Present evidence suggests, however, that febrile seizures generally do not predispose to recurrent spontaneous seizures but that this complication is dependent upon genetic or other acquired factors.

84. The Pediatric Management of the Muscular Dystrophic Child Based on Observations of Thirty Cases. LAWRENCE T. TAFT, M.D.* Department of Pediatrics, Albert Einstein College of Medicine, Yeshiva University, New York. Introduced by Henry L. Barnett.

The total management of the muscular dystrophic child should be the responsibility of the pediatrician. A need exists for cooperative planning with other specialists, but the pediatrician should be the person to whom the child and family go to for guidance, interpretations, and support.

To fulfill his role the pediatrician must have knowledge of the course of the disease and the presently available therapeutic techniques. The most important of the latter are knowledge of the psychosocial, educational, and economic factors which tend to affect the adjustment of the child and his whole family to this slowly progressive disease.

This paper will attempt to outline a pediatrician's experience and observations on the efficacy of certain management techniques in the problems of muscular dystrophics.

1. These conclusions are based on observations made over a period of four years on thirty muscular dystrophic children representing all stages of their disease. Thus, for example, the establishment of a recreational program for the nonambulatory dystrophics resulted in decreased withdrawal, better motivation, and less family tensions in a high percentage of cases.

2. The psychological implications of the disease on the child and his family will be discussed with recommendations as to prophylactic techniques to prevent, or at least, minimize emotional conflicts.

* By invitation.

Experiences of this clinic in the use of physical therapy, surgery, and medications will be compared to those reported in the literature. Finally, suggestions will be made in the prophylaxis of metabolic abnormalities that secondarily result from the prolonged immobilization that occurs late in the disease.

85. The Value of Cerebral Angiograms in the Diagnosis of Convulsive Disorders and Other Intracranial Lesions in Children. ALFRED UIHLEIN, M.D.,* and HADDOW M. KEITH, M.D. Sections of Neurological Surgery and Pediatrics, Mayo Clinic and Mayo Foundation, The Graduate School, University of Minnesota, Rochester, Minn.

Cerebral angiograms have been made for diagnostic purposes in 138 children. Seventy-one children were studied because of convulsive disorder with a suspected focus. Sixty-seven children were thought to have focal organic lesion, such as aneurysm, post-traumatic lesion or tumor, but did not necessarily have convulsions. The media used for injection were Diodrast and Hypaque. Complications were few, and none of them caused concern or prolonged the patients' hospital stay.

Among the 71 children with convulsive disorder primarily, angiograms indicated the presence of gross intracranial lesions in 6 cases. This is a relatively small number, but in two of these six cases tumors were demonstrated, and one was removed successfully. In the remaining four cases other lesions, such as porencephaly, were found. In 51 other children in this group the absence of gross lesion was demonstrated and suitable treatment could be planned. In the remaining 14 children the angiograms were unsuccessful and contributed nothing to the diagnosis. Thus in this group a definite diagnosis of gross intracranial lesion was shown in approximately 8.5% and the absence of such lesion in 71.8%.

Among the 67 children in the second group, 27 had definite gross lesions demonstrated by the angiograms, many of which lesions were amenable to surgical treatment. In 31 other children in this group, gross intracranial lesions were ruled out, and other treatment could be considered. In seven cases the angiograms were unsuccessful or of no value in making a diagnosis. Finally in two children the angiograms indicated gross lesions which were proved not to be present, when studied by other means. Thus in this group a definite diagnosis of gross intracranial lesion was made in approximately 40.3%, and the absence of such a lesion in 46.2%. In 3% "false positive" findings occurred, and in the remaining 10.4% the angiograms did not contribute any reliable information.

86. Pathogenesis of Paralysis in Hyperkalemic Familial Periodic Paralysis. R. KLEIN, M.D.; T. EGAN, M.D.,* and PATRICIA W. USHER, M.S.* University of Pittsburgh Medical School, Pittsburgh.

We have continued our investigations into the pathogenesis and physiologic changes in hyperkalemic familial periodic paralysis in four new patients, in addition to the three reported on last year. We have demonstrated striking shifts of extracellular and intracellular water, in addition to extending the observations on potassium changes reported on last year. The results of muscle biopsies done recently and the continued demonstration of excessive amounts of salt-losing hormone coupled with our previous findings enable us to arrive at a postulated mechanism for the production of symptoms in this disease.

Paralysis occurs in patients with hyperkalemic familial periodic paralysis when the subject rests after exercise (this is aggravated by the fasting state), when he ingests potassium, and when he is exposed to cold. In the first two situations, the extracellular potassium concentration is elevated. The mean increase in potassium in eight attacks was 29%, or over 1.2 mEq/L. However, potassium concentration may not be elevated beyond the extremes of normal variation. Presumably, the increase in ex-

* By invitation.

tracellular to intracellular ratio is the determining factor in this situation. Under experimental conditions, cold produces localized paralysis without increase in serum potassium. Preceding or coincident with attacks of either sort, there has been consistently demonstrated a decrease in plasma water of about 10%, with an equivalent increase in plasma protein and hematocrit. Simultaneously, there is a rise in red blood cell water concentration. There is no consistent significant change in serum osmolarity. In recovery, these changes reverse themselves, and in addition the sodium frequently rises. In the attacks marked by rising concentrations of extracellular potassium, the increase cannot be accounted for by the loss of extracellular water. The elevation of extracellular potassium is associated with negative peripheral A-V differences of the ion about 50% of the time. This indicates release of potassium from skeletal tissue. Nonskeletal tissue may be involved as the source of the potassium entering the extracellular compartment part or all of the other times. In recovery, the potassium is always taken up by nonskeletal tissue. The only change in the variables measured when attacks are abruptly ended by the administration of glucagon, epinephrine, or DL-amphetamine, is a rapid fall in extracellular potassium.

Two muscle biopsies on one of these patients showed low intracellular potassium concentrations and relatively high sodium and water concentrations. Potassium concentrations were 128 and 139 mEq/kg. of intracellular water in the two specimens. The mean for seven controls was 159±8.1. Intracellular water concentration was increased to a level of 290 ml. per 100 gm. of dry, fat-free solids. The mean for normal controls was 235±27.8.

At the present time we tentatively explain these facts as follows: The excess salt-losing hormone leads to a frequent or constant slight depression of intracellular potassium. Any increment to extracellular potassium produced in the normal fashion by ingestion, glycogenolysis, muscular activity, or normal diurnal variation is enough to raise the extracellular to intracellular potassium ratio sufficiently to produce paralysis. Alternatively, when intracellular water and sodium are increased, as upon exposure to cold, the intracellular potassium concentration is lowered, thus raising the ration of extracellular to intracellular potassium, and the effect of this is aggravated by the reciprocal change in extracellular to intracellular sodium ratio. In this situation, too, we feel that the inhibition of influx of potassium into the cell is of primary importance.

87. Treatment of Infantile Myoclonic Seizures with Corticotropin and a Corticosteroid. JUNE M. DOBBS, M.D.*; JAMES D. CLEMENTS, M.D.,* and H. W. BAIRD, M.D.* Department of Pediatrics, Temple University School of Medicine and St. Christopher's Hospital for Children, Philadelphia. Introduced by John B. Bartram.

Recently, Sorel (*Acta neurol. et psychiat. belg.* 58:130-141, 1958) and Low (*Pediatrics* 22:1165-1169, 1958) have given corticotropin and cortisone to children with infantile myoclonic seizures and have reported encouraging results. Similar data have been collected by Stamps, Gibbs, and Gibbs (*Proceedings of the Brain Research Council,* March 31, 1958, Chicago). During the past 15 months, we have used this treatment on 26 children. Our results have not been conclusive.

Each child was started on corticotropin, 10 units a day for 15 days. This course of therapy was repeated in seven days if the initial course had not been beneficial. More recently, corticotropin has been administered in increasing doses up to 50 units a day for a period of 30 days. Some children have received prednisone, 1 mg. per pound per day, as an alternative to the increase doses of corticotropin.

Four children who were thought to be completely normal before they began to have

* By invitation.

myoclonic seizures were treated with corticotropin and prednisone. They ranged in age from 5 to 12 months. One child stopped having seizures, but the EEG has remained abnormal and she has made no developmental progress. One child stopped having seizures, has a normal EEG, but has a right hemiplegia and developmentally is only 75% of normal; although he is hyperactive, he seems to be making developmental progress. One child stopped having seizures while receiving corticotropin and remained seizure-free for a period of two and a half months; recently; however, they have recommenced. He is very hyperactive and has made no developmental progress other than improved gross motor activity since the last seizures began. One child stopped having seizures, has a normal EEG, and at 9 months of age appears to be developmentally normal.

Five children who were thought to have brain damage before the onset of seizures were given corticotropin for 30 days and prednisone without effect.

Four severely retarded children who have had seizures for many months were given corticotropin and prednisone. Each of them stopped having seizures, now has a normal EEG, and, although still severely retarded, appears much more responsive and alert. Two of them actually have made some developmental progress.

Seven older children who have had seizures for many years derived no ulimate benefit from such therapy.

Six children in the age range of 3½-10 years who had myoclonic seizures and a modified hypsarhythmia as demonstrated by EEG were treated with corticotropin and prednisone; in only two of these, in whom seizures ceased following therapy, has there been any benefit. Both of them received prednisone.

Thus, in our hands, corticotropin and corticosteroid therapy for infantile myoclonic seizures has been associated with variable clinical responses. Two infants who were so treated within a few weeks of the onset of myclonic seizures are apparently seizure-free and are making developmental progress. However, it is very difficult to evaluate the significance of their present developmental ability. We have previously commented (*J. Pediat.* 50:332-339, 1957) upon the excellent gross motor ability which many such children ultimately exhibit; only time will tell whether or not these two children will improve in their adaptive behavior. It is also difficult to evaluate the role played by corticotropin and corticosteroid therapy in the improvement observed in four children who had had seizures for many months. From past experience we would not have expected all four to have stopped having seizures so promptly without therapy.

Our present plan is to employ corticotropin and corticosteroid treatment in patients with infantile myoclonic seizures, since any other form of therapy offers so little to these children. However, the results have not been as encouraging as anticipated, and information concerning the possible mechanisms by which such therapy might influence these children is not available.

88. Endocrine and Metabolic Observations in Children with Craniopharyngiomas Before and After Surgical Treatment. JOHN F. CRIGLER JR., M.D.*; DONALD D. MATSON, M.D.,* and ANN E. NIALL, M.D.* Department of Pediatrics, Children's Hospital, Harvard Medical School, Boston. Introduced by William Berenberg.

During the past five years total removal of craniopharyngioma has been attempted in 10 patients between the ages of 4 and 12 years. Such extensive surgery, made possible by the availability of adrenocortical hormones, has introduced new problems in medical management resulting from alterations in hypothalamic and pituitary function.

Evaluation of neurohypophyseal thyroid, adrenal and gonadal function has been made preoperatively in seven patients and postoperatively in 10.

Preoperatively, one patient had evidence of diabetes insipidus with inability to con-

* By invitation.

centrate urine above a specific gravity of 1.013 with a 12-hour water fast. Hypothyroidism, as determined by altered Growth pattern, retarded skeletal maturation, and decreased P81 and BMR, was clearly evident in only one patient. It is interesting, however, that skeletal maturation was 1 to 4 years behind the chronological age in the seven patients having preoperative wrist x-rays. Preoperative adrenal function as determined by urinary and plasma 17-OH-corticoids was within normal limits. Only one patient was in the adolescent age range preoperatively and he showed evidence of early adolescent development with hormonal studies appropriate for his chronological age and degree of sexual maturation.

Immediately after operation all 10 patients had polyuria and polydypsia with urinary specific gravities below 1.010. In six diabetes insipidus has persisted, requiring Pitressin therapy. Two patients recovered from early postoperative diabetes insipidus, and two have developed marked, persistent hypernatremia complicating the evaluation of salt and water metabolism. The mechanism of the lesion in the latter two patients which appears to be hypothalamic in origin is being further investigated. Six patients showed marked lowering of the PBI following surgery, and two others had PBI's under 3.5μg. %. These patients required thyroid therapy. Adrenal function immediately after operation is diffcult to evaluate owing to cortisone administration for surgery. When cortisone is discontinued, values of both urine and plasma 17-OH-corticoids tend to be abnormally low—at times not detectable in plasma. Seven patients, at present, however, are receiving no substitution therapy. Because of patients' ages, postoperative evaluation of gonadal function is uninformative to date.

Nine of the ten patients have shown an excellent response to the surgical and medical therapy. One patient who required two operations for the removal of an extensive lesion still remains limited in activity and has lost her vision.

89. Growth and Development of Negro Infants: Weight, Height, Pelvic Breadth, Head and Chest Circumference from Birth to One Year. ROLAND B. SCOTT, M.D.; ALTHEA D. KESSLER, M.D.*; BETTIE G. CLARK, M.D.*; HOWARD H. HIATT, A.B.,* and ANGELLA D. FERGUSON, M.D.* Department of Pediatrics, Howard University College of Medicine and Pediatric Service of Freedmen's Hospital, Washington, D. C.

The population studied consisted of Negro infants who attended the Well Baby Clinic of Freedmen's Hospital from 1950 to 1956. Approximately 60% were bottle fed, 20% breast and bottle fed, and 20% breast fed. All received vitamins at about 1 month and a semisolid food at about 2 months of age. In general, the self-demand technique of feeding was encouraged.

The sample for each measurement was obtained by selecting from our records all cases for which there were enough recorded determinations to support linear interpolation of monthly values from birth through 12 months. The sizes of the samples are as follows: for males, weight 39, height 34, head circumference 32, chest circumference 20, pelvic breadth 19; for females, weight 52, height 47, head circumference 41, chest circumference 24, pelvic breadth 26. After interpolation, monthly means and standard deviations were computed and growth curves were drawn for comparison with those obtained by other investigators. Our curves were compared with those of Vickers and Stuart (1943) for white infants and with those of Kelley and Reynolds (1947) for white and for Negro infants.

Negro male and female infants weighed slightly less at birth. Negro males weighed more than white infants between the 3d and 12th months. Negro females weighed more at 12 months.

* By invitation.

Mean Measurements at the Extremes and Midpoint of the Study Period

Age	Weight		Height		Pelvic Breadth		Head Circumference		Chest Circumference	
	Kg.	Lb.	Cm.	In.	Cm.	In.	Cm.	In.	Cm.	In.
					Male					
Birth	3.3	7.2	49.7	19.6	9.1 *	3.6	33.9	13.4	32.0	12.6
6 mo.	8.1	17.9	68.2	26.9	11.3	4.5	43.2	17.0	42.6	16.8
12 mo.	10.6	23.4	76.9	30.3	12.7	5.0	47.1	18.6	46.7	18.4
					Female					
Birth	3.3	7.2	49.4	19.5	8.9 *	3.5	33.9	13.4	32.7	12.9
6 mo.	7.6	16.8	66.2	26.1	11.0	4.3	42.7	16.8	41.9	16.5
12 mo.	10.1	22.2	75.0	29.6	12.3	4.8	46.0	18.1	45.8	18.0

* Mean at 1 month of age.

Negro infants were shorter at birth but presented essentially the same stature curve after 3 months as the white infants.

Both male and female white infants had wider pelves than the Negro infants in our series.

The Negro infants in this study had a smaller head circumference at birth but presented a growth curve similar to that of the Kelly-Reynolds series on Negro and white infants.

Chest circumference was smaller at birth for our Negro infants. Throughout the remainder of the first year our values were larger than those reported for Negro and white infants in the Kelly-Reynolds series, but smaller than those reported for white infants in the Vickers-Stuart study.

90. Chronic Constipation in Childhood. GIULIO J. BARBERO, M.D.*; MARY BROOKS, A.B., M.A.*; IH CHIM KIM, M.D.,* and MARIAN G. MORRIS, B.S., M.S.W.* The Children's Hospital of Philadelphia and the Department of Pediatrics, School of Medicine, University of Pennsylvania, Philadelphia. Introduced by T. F. McNair Scott.

Since the delineation of the aganglionic lesions in Hirschsprung's disease, there have been a number of studies of the remaining large group of children having constipation without this lesion. Garrard and Richmond have defined certain clinical characteristics of these cases differentiating them from those with aganglionic megacolon. Their study and those of others have led to the impression that constipation in these children is a manifestation of emotional disturbance.

The present study of 50 children with severe chronic constipation was undertaken to obtain further data on the clinical picture and also information on the physiological manifestations. Hospitalization was carried out in all patients. Aganglionic megacolon was ruled out by x-ray examination. Rectosigmoid motility studies were carried out at the beginning and end of hospitalization. The play activity of the children was observed and recorded.

The following findings were encountered. The onset appeared in the first year of life in 50% of the cases. The onset was described as precipitated by some experience such as hospitalization for illness or operation and acute separation from the family resulting from parental illness or conflict in 30%. The ratio of boys to girls was 4:1. The complaint of constipation was found most frequently in the second child of the family. Fecal soiling was present in 66% and usually followed a period of constipation. The fecal soiling could not be described as "diarrhea" around an impaction but rather consisted of small amounts of soft feces found in the dilated rectum. Abdominal pain was present in 75% of

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the cases. Feeding difficulty, which became more pronounced at the height of constipation, was a complaint in 66%. In 78% the mother had had one or more pregnancy disturbances manifested as physical illness or severe emotional reaction. In more than 66% there were major reality social situations in the family history, such as divorce, separations, threatened separations, and deaths in the family. A consistent pattern of play activity was observed and will be described. Following hospitalization 95% of the children had daily bowel movements without assistance. This symptomatic change had a wide range in duration, varying from a brief period of one month to as long as five years. Further follow-up evaluation will be reported. The rectosigmoid motility demonstrated no evidence of an atonic bowel but rather an increase in wave frequency, tonus, and total activity. Quantitative analysis of these recordings and comparison with a control group will be presented.

91. The Problem of Parental Criminal Neglect and Severe Physical Abuse of Children. C. HENRY KEMPE, M.D., and HENRY K. SILVER, M.D. Department of Pediatrics, University of Colorado School of Medicine, Denver.

The recognition of criminal neglect and physical abuse of children requires a certain degree of realistic open-mindedness on the part of the pediatrician, who may, on emotional grounds, tend to reject the concept that parents can and do severely neglect or physically harm their children. A number of recent instances of criminal neglect and severe physical assault in more than one sibling in a family will be briefly reviewed. These cases illustrate that the pediatrician must have an awareness of the problem when the first instance of abuse in a family occurs so that he may be prepared to make a specific diagnosis and recommendations that will lead to the institution of protective measures for the remaining children. The frequent failures of physicians, social services, and the law, in coping with felonious neglect and physical abuse of a degree that leads to severe injury or death, require a frank reappraisal of this difficult problem.

92. A Combined Study of Learning Disabilities in Children: A Progress Report on the Neurological and Physical Findings. PAUL R. PATTERSON, M.D.*; RUTH H. SOLOMON, M.A.*; MORTON I. WEISER, PH.D.*; LENORE SPORTSMAN, M.D.*; FREDERICK D. MCCANDLESS, M.D.*; DOROTHY MOYER, A.B.*; PHYLLIS R. SANDS, M.S.*; EMILY K. KENFIELD, M.A.*; MORRIS E. ESON, PH.D.*; J. ROY NEWTON, ED.D.*; FREDERICK HESSER, M.D.*; STANLEY M. BALL, M.D.,* and RUTH SHEERAN, M.S.* Albany Medical College, of Union University, Albany, N. Y. Introduced by Charles A. Janeway.

Children of normal or above normal intelligence who have difficulty in learning or reading are being studied by a combined team of educators, psychologists, psychiatrists, pediatricians, endocrinologists, neurologists, ophthalmologists, and social workers.

All causal and concomitant factors—neurological, physiological, psychological and environmental—related to inadequate school achievement among these children is being studied thoroughly. These studies range from a battery of individually administered intelligence, aptitude, and achievement tests to more complex electroencephalographic studies and biohormonal urinary assays and projective psychological tests.

This project was stimulated by the finding of a large percentage of boys who were brought before the children's court with the history of difficulty in learning in school. Likewise, it was found that from 5% to 15% of elementary school children were unable to function at their grade level and to their full capacity and ability to achieve as expressed by psychological testing, e. g.,

* By invitation.

a child with 118 I. Q. in Grade 6 reading on a Grade 1.2 reading level.

Eighty-three children whose ages range from 7 years through 18 years were tested. Seventy-nine of these significantly were boys. The intelligence test scores ranged from 65 to 132. The medium grade level for referral was 4.4, while the range extended from the first through the ninth grade. Sixty-eight subjects tested with the Gray Oral Reading Test gave the median as three grade levels below the actual grade placement. The range extended from the first grade up through mid fourth grade.

All of the children displayed some emotional difficulties of adjustment in one form or another. One-third of the puberty-age boys manifested gynecomastia. Nearly 50% of all the boys appeared to have genitals resembling boys several years younger than their given ages. While many gave the history of difficulty in performing adequately in athletic sports, very few presented with abnormal neurological findings.

Preference tests given to indicate the children's preference for right or left appendage or organ were made to appraise the dominance of the hand, foot, eye, and ear. Five per cent were left dominant. Sixty-seven per cent of sixty-one cases showed mixed laterality. Twenty-eight per cent were right dominant. A number of the children at all ages were unable to distinguish their right from their left sides.

Sixty-four per cent of the electroencephalographic findings were definitely abnormal; another sixteen per cent of the records were read consistently as borderline, and twenty per cent were considered to be normal.

The abnormal readings were broken down into three categories: those where diffuse encephalopathy was found; those where localization was obvious, and the third where both diffuse and localized encephalopathy was found. The correlation and localization of the electroencephalographic findings with the psychological testing and hormonal studies and physical findings are discussed.

There is evidence that a large percentage of children having learning difficulties in school and presenting themselves as emotional psychological problems may well have minimal brain damage.

93. Attempts to Influence Phenylalanine Plasma Levels by Oral Feedings. HARRY A. WAISMAN, PH.D., M.D., and HWA L. WANG, PH.D.* Department of Pediatrics, University of Wisconsin Medical School, Madison, Wis.

Preliminary work reported from this laboratory has demonstrated that feeding amino acids to rats can influence the *fasting* levels of amino acids. In the present study the effects of phenylalanine and/or tyrosine feedings on their plasma levels were studied in dogs and monkeys. In the first experiment, dogs were fed 3.75% DL-phenylalanine, 3.75% L-tyrosine or 3.75% DL-phenylalanine and 3.75% L-tyrosine. After five weeks on these diets no change in plasma phenylalanine and tyrosine levels was observed. Ten dogs were used in the second experiment; six dogs were fed 10% DL-phenylalanine, and four kept on regular dog chow as controls. Growth was lower in those dogs fed amino acids when compared with control animals. The phenylalanine blood level remained normal after 13 weeks in all dogs, and the tyrosine level was unchanged except in two dogs on the phenylalanine diet which showed unusually high levels.

In an effort to get additional information in other animals, it seemed advantageous to perform similar experiments on monkeys. Two monkeys each were fed an adequate diet plus daily supplements of (1) L-phenylalanine, (2) L-tyrosine, and (3) both amino acids. Feeding L-phenylalanine definitely raised the fasting plasma level of both phenylalanine and tyrosine, but feeding L-tyrosine alone did not influence the blood phenylalanine level. When L forms of both amino acids were fed, the phenyl-

* By invitation.

alanine increased slightly while the tyrosine was markedly increased. An interesting observation was made during the time the quantity of the amino acids was increased in the diet. The first week after double amounts of L-phenylalanine were fed, the blood levels were elevated, but then they dropped back to lower levels within three to four weeks. When the quantities of phenylalanine were tripled, the blood levels in one of the two monkeys fed phenylalanine increased to even higher levels and remained there, while the other monkey showed only a slight increase, still above normal, however. Consideration of the theory of negative feedback and positive feedback and how it applies to these findings will be given.

The urine was tested for phenylpyruvic acid and for other amino acid metabolites. The monkeys were also tested for discrimination ability, and an attempt made to correlate increased blood phenylalanine levels with some intellectual performance tests.

94. Long-Term Follow-Up of Children and Adults Exposed to Repeated Fluoroscopic Examinations (1920-1958). ANN MCA. BIRCH, M.D., M.P.H.,* and DAVID H. BAKER, M.D.* Department of Pediatrics, New York Hospital-Cornell Medical Center, New York. Introduced by May G. Wilson.

The recent emphasis on potential hazards of serial fluoroscopic examination for diagnosis has deterred its use in most pediatric centers. This study is concerned with a review of the records of patients and their progeny for whom serial fluoroscopic examinations in the clinic were recorded over the past 38 years. There were approximately 1,500 persons—adults and children—who received an average of 15 to 20 serial fluoroscopic examinations during the period of observation for an average exposure of 10 r each. The incidence of cancer, leukemia, congenital malformations, and stillbirth were found to be no more than would be expected in the general population.

It is concluded that no evidence of deleterious effects was obtained in patients or their progeny exposed to serial fluoroscopic examinations during a 38-year period.

95. Study of the Irradiation Protection Effect of Pooled Fetal Liver in Mice. JOHN H. GITHENS, M.D.,* and LEONE ST. VINCENT.* Department of Pediatrics, University of Colorado, Denver. Introduced by C. Henry Kempe.

Previous studies have shown that fetal liver can be used as a source of hematopoietic tissue for protection against the lethal effects of total body irradiation. In the present study, the radiation-protection effect resulting from the administration of varying doses of nucleated cells from homologous fetal and newborn liver tissue given to 6- to 9-week-old Webster mice has been investigated. The protection obtained by the injection of various preparations and components of liver (including cell-free homogenate) have also been studied. All animals received lethal doses of total body irradiation prior to intravenous infusion of the liver preparations. The irradiation dose in most of the experiments was 700 r, although in some instances, comparable studies were carried out with 600 r and 650 r (600 r being the MLD_{100}). The basis of comparison of the effectiveness of various doses and tissue preparations was the 24-day mortality of the irradiated mice.

Protection following administration of washed intact nucleated liver cells was found to be related to the cell dose. The optimum cell dose was approximately 20,000,000 cells per animal; this resulted in a mortality of only 33% (as compared with a mortality of 100% in unprotected animals). No protection could be obtained with 4,000,000 washed cells, while a massive dose of 100,000,000 washed cells gave less protection (with mortality rates of 60% to 100% depending on the irradiation dose

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used) than was obtained after the injection of the 20,000,000 washed cells.

Administration of complete liver tissue after passage through screens which divided the tissue into single-cell particles resulted in an immediate mortality directly attributable to the injection itself, but gave up to 50% protection in those animals surviving the injection after infusion of a sample containing 4,000,000 cells. When the inoculum contained 22,000,000 cells, better protection was obtained than with an equivalent dose of washed cells. The administration of a sample containing 100,000,000 cells resulted in a prohibitively high mortality from the injection.

The infusion of cell-free washings are not attended by any protection, even though the preceding results suggest that the washings in those experiments may have contained some of the radiation-protection factor. Administration of washed nuclei from which most of the cytoplasm had been removed gave no protection, but a "cell-free" liver homogenate produced a slight but increased survival rate.

Certain implications of these studies will be discussed.

96. Tracheal Fenestration: A New Treatment for Chronic Pulmonary Disease. E. E. ROCKEY, M.D.,* and EDWARD WASSERMAN, M.D.* Department of Thoracic Surgery and Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals, New York. Introduced by Lawrence B. Slobody.

In the treatment of chronic pulmonary diseases, e. g., in mucoviscidosis, the removal of thick tenacious secretions from the tracheobronchial tree often presents a difficult problem. The currently available mechanical methods for removing secretions, e. g., tracheotomy, bronchoscopy, and exsufflation interfere with the physiologic functioning of the respiratory tract.

Tracheal fenestration has been developed through extensive animal experiments. It is a surgically created, skin-lined communication from the trachea of the anterior surface of the lower portion of the neck. The skin orifice is provided with two door-like skin valves which make the communication airtight unless the valves are pulled apart. The valves can be opened manually for the purpose of administering medication or for repeated tracheobronchial aspirations which eventually can be performed by the patient. Patients with tracheal fenestration continue to breathe through the nose so that the inspired air is normally warmed and moistened. Phonation and cough mechanism, too, remain undisturbed.

Tracheal fenestration has been performed on 24 adult patients. All of these patients were confined to bed or home because of very severe respiratory insufficiency with progressive obstruction to the airways due to retained thick, tenacious secretions. Reported tracheobronchial aspirations (as many as 50 or more times per day) following the operation resulted in the removal of copious amounts of secretions. Some improvement was apparent in all patients and eight were rehabilitated sufficiently to permit them to be gainfully employed or to resume full household duties. There were no operative deaths. (A short moving picture film will be shown of patients before and after surgery.)

Tracheal fenestration and repeated tracheobronchial aspirations were performed on a 5½-year-old child with pulmonary failure due to mucoviscidosis. The child died subsequently. However, the clinical course suggests that tracheal fenestration for repeated tracheobronchial aspiration and administration of medication is practical in children. Its possible use should be studied further in cases of severe progressive peripheral airway obstruction associated with retained viscid secretions.

* By invitation.

Abstracts from Current Literature

A. M. A. Archives of Internal Medicine, Chicago

Abstracted by Philip N. Jones, M.D.

102, No. 5 (Nov.) 1958

Nasal Carrier Rate of Antibiotic-Resistant Staphylococci. W. R. O. Goslings and K. Büchli.—p. 691.

A Follow-Up Study of Hereditary Chronic Nephritis. G. T. Perkoff, C. A. Nugent Jr., D. A. Dolowitz, F. E. Stephens, W. H. Carnes, and F. H. Tyler.—p. 733.

* Sarcoidosis. H. L. Israel and Maurice Sones.—p. 766.

* Cryptococcal Meningitis Treated with Amphotericin B. John A. Gantz, John A. Nuetzel, and Louis B. Keller.—p. 795.

* An Agent Effective Against Cryptococcosis of the Central Nervous System. Arthur Biddle and Harold Koenig.—p. 801.

The Isolation of Adenovirus Type I from a Fatal Case of Viral "Pneumonitis." Friedrich Deinhardt, Robert D. May, Hugh H. Calhoun, and H. E. Sullivan.—p. 816.

Treatment of Tetanus. Gabriel Kourany, E. A. Cleve, and Frank B. Smith.—p. 823.

102, No. 6 (Dec.) 1958

Results of Mitral Commissurotomy. F. Henry Ellis Jr., Daniel C. Connolly, John W. Kirklin, and Robert L. Parker.—p. 928.

The Management of Hospital-Acquired Staphylococcal Infections. Ellard M. Yow, Martha D. Yow, G. Kenneth Womack, Toru Sakuma, and Ofelia T. Monzon.—p. 948.

Experience with Amphotericin B for Treatment of Systemic Mycoses. John H. Seabury and Harry E. Dascomb.—p. 960.

Sarcoidosis.—This article is a general review of the different aspects of sarcoidosis. The authors point out that this disease has become in Scandinavia and Eastern United States a very common one and the number of reported cases have been increasing. In Sweden between the years 1950 and 1954, there were detected almost half as many cases of sarcoidosis as of tuberculosis. It is still not clear whether this is due to better recognition or whether sarcoidosis is actually increasing. The authors report their observations with 160 patients who had been seen between 1938 and 1956. All of these cases had one or more biopsies demonstrating epithelioid tubercles. Of these patients, 25 were under the age of 21. The mortality rate was 8.1%, two deaths due to tuberculosis and the other eleven due to progressive sarcoidosis. The only agents which have proved of value are the corticosteroids: cortisone and its derivatives and corticotropin. Complete clearing of symptoms and radiologic changes were observed in 34.2% and an additional 27.4% were classified as improved. The effect on some manifestations of sarcoidosis is dramatic, especially those with uveoparotid fever. The effect of mediastinal adenopathy, on the other hand, may be minimal. Symptomatic improvement is obtained in most cases.

Comment: This is a good review article, and the general features are discussed, as well as the problems which are presented when the disease hits the various systems of the body. The authors point out that the term "sarcoidosis" is a clinical diagnosis and is one that cannot be made, nor should it be made, by the pathologist. The diagnosis requires in addition to the demonstration of histologic changes, clinical and radiologic evidence as well as careful exclusion of diseases that simulate sarcoidosis.

Cryptococcal Meningitis Treated with Amphotericin B.
An Agent Effective Against Cryptococcosis of the Central Nervous System.

These two articles, one submitted from St. Louis and the other from Chicago, deal with the results of the drug Amphotericin B in the treatment of cryptococcosis. There are three cases of cryptococcal meningitis reported, all of which were successfully treated with this drug. One of the cases finally ended fatally although there was complete clearing of the organisms. The other two cases have at least been arrested and are clinically well at the time of this report. Longer follow-up periods are necessary to be sure that the drug has effected a permanent cure. These reports are encouraging and this drug is recommended in this condition which is almost universally fatal if not treated. There has been very low toxicity to

* These articles are abstracted in this issue.

this drug. Large oral doses were tolerated without gastrointestinal symptoms. There was symptomatic improvement on the oral dosage but it is advised that the intravenous therapy must be used to completely eradicate the organism.

Archiv für Kinderheilkunde, Stuttgart

Abstracted by Werner K. Gottstein, M.D.

158, No. 1, 1958

On Transitory Alterations of Excitatory Retrogression in the Electrocardiogram of the Child. G. Leutz and H. Klepzig.—p. 7.

* The Adrenogenital Salt-Loss Syndrome of Salt. R. Schaefer and F. Souchon.—p. 17.

On the Pathogenesis and Therapy of Tuberculous Meningitis in Childhood. K. B. Choremis.—p. 46.

The Usefulness of the Uropepsin Test for the Examination of the Function of the Suprarenal Cortex in Prematures During the First Three Months. H. Hingkeldey.—p. 56.

Contribution to the Clinical Entity Osteogenesis Imperfecta. H. G. Detmold and H. Wolf.—p. 60.

Retrogression of a Severe Mediastinal and Skin Emphysema Under Oxygen Inhalation. E. Doll and J. Wenner.—p. 64.

Mediastinal Emphysema Complicating Measles. I. Weber.—p. 72.

158, No. 2, 1958

Experiences with Protracted Cortisone Treatment of Nephrosis in Childhood. H. Hanssler.—p. 110.

On an Epidemic of Abacterial Meningitis. K. Nissler and A. Regitz.—p. 121.

On the Stevens-Johnson Syndrome. Christel Juntke.—p. 129.

The Serological Diagnosis of Grippe in Infancy. O. Vivell and F. Schröpl.—p. 135.

Possibilities and Limitations of the Phenol Red Test in Renal Diagnosis. Gertrud Marquardsen.—p. 142.

On Syndactylia in Childhood. G. Mülke and D. Helbig.—p. 153.

Bilateral Wilms Tumor. Ilse Wolfrom.—p. 159.

Amaurosis and Hemiparesis After Typhoid in a 3-Year-Old Child. R. Glander and H. Illert.—p. 164.

Recurrent Chickenpox Under Treatment with Cortisone and Prednisone. B. Dransfeld.—p. 70.

158, No. 3, 1958

Critical Investigations Concerning Bifidogenous Mixtures and Supplements. H. Gross and K. Macho.—p. 214.

Comparative Study of the Untoward Effect of Water- and Oil-Soluble Vitamin K Preparations in Prematures. Sükran Yalcindag.—p. 228.

Electrocardiographic Examinations of the Dying Heart of the Child. H. W. Kirchhoff.—p. 238.

A Simple and Rapid Method for the Diagnosis of Pathogenic Coli in Smears of the Feces by Fluorescent Antibodies. F. Petuely and G. Lindner.—p. 248.

Periston N in the Treatment of Icterus in Prematures. G. Wohlmut and P. Kiss.—p. 253.

School Difficulties and Pediatric Practice. H. Hartenstein.—p. 256.

Two Observations Concerning the Genetics of Anal Atresia. W. Fuhrmann, A. Rieger, and F. Vogel.—p. 264.

Dysostosis Cleidocranialis or Dystostosis Generalisata? W. H. Buhn and R. Beckmann.—p. 270.

159, No. 1, 1959

Macroglobulin Determinations in Serum of Healthy Children During the First Year of Life. F. Koch, H. E. Schultze, and G. Schwick.—p. 3.

Thermoelectric Determinations of the Temperature as Diagnostic Procedure in Latent Inflammatory Foci in Childhood. P. Biesalski.—p. 8.

The Hyperketonic Diabetic Coma and Its Treatment in Childhood. H. G. Krainick and M. Tittmann.—p. 15.

The Incidence of Antibodies in Grippe Virus Type D. O. Vivell, G. Reimold, and H. Yoshioka.—p. 28.

* Studies of Morphologic Alterations in the Rabbit Heart by Streptococci and Streptococcic Infiltrations. R. Gädecke and W. Marget.—p. 38.

Metabolism and Regulation of Hemoglobin in Childhood. K. Betke.—p. 51.

The Incidence of Enteral Cytopathogenic Virus in Abacterial Enteritis in Infancy and Childhood. R. Sauthoff.—p. 67.

Results of Balance Tests to Determine the Value of the Second Carbohydrate in Infant Nutrition. R. Beckmann.—p. 75.

Ammonia and Acid Excretion in the Urine in Childhood. H. Hungerland and R. Schulz.—p. 88.

Adrenogenital Salt-Loss Syndrome.—These observations were made in seven infants (five girls and two boys, brothers and sisters) who showed adrenogenital salt losses. The initial signs were anorexia and vomiting and appeared between the 7th and 58th day after birth. Acute and almost fatal failures of the mineral metabolism are demonstrated in detailed curves. The observation period lasted from five months to three and a half years. The case of the longest observation period terminated fatally postsurgically. The authors emphasize that the correction of salt depletion represents the most important therapeutic method. The additional treatment with cortisone was imperative in only one case.

Studies of Morphologic Alterations in the Rabbit Heart by Streptococci and Streptococcic Infiltrations.—Killed or live streptococci of different β-hemolysin producing strains (A,C,G) were given to rabbits over different periods of time. After short-term

application of live bacteria, endocardial edema, myocardial necrosis, fibrinoid or eosinophilic degeneration appeared. In some coronary vessels, streptococcic emboli were observed. Likewise, proliferative reactions were present in the vascular walls. Following parenteral applications of filtrates from bacterial cultures as well as live bacteria, serous inflammatory endocardial reactions could be demonstrated, also myocardial granulomas, and finally perivascular fibrosis and parietal coronary reactions. Such histological alterations are comparable to specific rheumatic changes.

This is a very comprehensive paper with excellent colored prints that demonstrates again the experimental identity of rheumatic histology and injection of filtrates. The paper affirms previous statements of Roessle, Klinge, and Rich. Therefore, this contribution obviously affirms the theory of the classification of collagen diseases. However, it must be taken into consideration that the collagenous connective tissue can only react in the histological picture by nondiversified alterations and by a variety of stimuli.

Medical Journal of Australia, Sydney

Abstracted by George H. Lowrey, M.D.

1, No. 1 (Jan. 3) 1959

Thirty Years of Juvenile Rheumatism. Laurence Hughes.—p. 7.

1, No. 2 (Jan. 10) 1959

Fluid and Electrolyte Metabolism in Childhood in Health and Disease. W. B. Macdonald.—p. 35.
Some Aspects of the Nephrotic Syndrome in Childhood. Robert Vines.—p. 42.

1, No. 5 (Jan. 31) 1959

Recent Advances in Viral Infections of Childhood. Frank Fenner.—p. 137.
Some Principles in the Management of Emotional Disorders of Children. Winston Rickards.—p. 140.
Arthur Jeffreys Wood: A Paediatric Profile. Howard Boyd Graham.—p. 144.
* The Contribution That Might be Made by the Paediatrician and General Practitioner to the Management of Delinquency. Alan Jennings.—p. 146.
Experiences in the Application of Principles: Food Refusal. Felix Arden.—p. 147.
Renal Infarction and Perirenal Haemorrhage. T. Y. Nelson.—p. 148.
Peptic Ulceration in Childhood. Eric Goulston.—p. 150.
Bilateral Congenital Choanal Atresia in the Newborn. Peter Jay.—p. 151.
Medical Aspects of Pyuria in Childhood. John McDonald.—p. 152.
Chronic Pyuria in Children. F. Douglas Stephens.—p. 154.
* Primary Tuberculosis: Is Chemotherapy Necessary? Douglas Galbraith.—p. 155.
Acute Subdural Haematoma in the Newborn. M. Sofer Schreiber.—p. 157.
Australian Paediatric Association—Abstracts of papers presented.—p. 164.

The Contribution That Might Be Made by the Paediatrician and General Practitioner to the Management of Delinquency.—The author states that for the sake of simplicity, delinquency in children may be roughly divided into three categories: (1) delinquent behavior occurring when there is no marked psychological abnormality, that is, when social maladjustment reflects adverse external circumstances; (2) delinquent behavior occurring in an emotionally disturbed child when the emotional disturbance is a reaction to environmental difficulties; (3) delinquent behavior associated with maladjustment that has become chronic and built into the personality. It is felt that the severer problems are apt to come from the complex and materialistic urban community where religious influences would appear to have less force and where the moral codes are less well defined. It is also in such a community that individuality and freedom are encouraged, sometimes at the expense of good supervision or guidance to the older child. In the rural area, there is apt to be a simpler society and a more rigid and clear-cut framework for behavior which the child can more easily follow. The author states that the delinquent may often be a fairly happy adventurous boy who looks for personal gain in acts of minor delinquency. Such children are more likely to commit their offenses in company and usually are capable of making a good social relationship, and response is usually adequate to a simple warning and better supervision. When there is a greater degree of emotional disturbance, one usually finds that there are a number of internal and external stresses upon the child. A vicious cycle is apt to be established in which insecurity and anxiety promote aggressive and delinquent behavior. The child has some guilt about this and more anxiety, and as a result of this he is apt to become still more aggressive and find himself in further delinquencies. The author points out that such children are apt to be tense and anxious. They often suffer

from disturbances in sleep and speech disorders; they frequently are restless and overactive and impulsive in their activities and lacking in an ability to concentrate. Frequently they have difficulty at school; they are often immature in their emotional reactions, showing temper tantrums when attempts are made to curb their activity. The parents of such children may fit into many different categories; however, it is emphasized that often these parents are hostile or rejecting of the children, resulting in the child who is overly attention seeking. Another large group are the children of perfectionist parents. Such children are often immature and overdependent upon their overprotective parents. In either type of parent, there may be an unconscious attempt to encourage the amoral and antisocial behavior of the child by the parent. This appears to be a neurotic escape mechanism on the part of the parent who desires a vicarious gratification. Occasionally the child is actually dull or below average intelligence and has specific educational defects. Other constitutional or organic abnormalities may be found in such children.

The treatment of such children is not a simple thing, but the author points out that often, if the physician is willing, he can be of great assistance. In the emotionally disturbed child, he may be in a position to help the child manage his difficulties. The child may have to talk at considerable length and feel accepted before he can reveal his feelings, but when he does he can be helped to tolerate his anxiety, tensions, and unhappiness, and therefore have less need to act out his problem in an antisocial way. Evaluation of the parents in any such situation is obviously of extreme importance. Many times the parents will require psychotherapy, and it may occasionally be necessary to have the child removed from the home situation during this time. So far as prognosis is concerned it must be decided whether the symptoms are reaction to environmental difficulties or whether they are the result of a well established and internalized conflict. In the latter case, it is found that the children often are inflexible, unrealistic, and unresponsive to ordinary management programs, and specialized psychotherapy will be required to treat them.

Primary Tuberculosis: Is Chemotherapy Necessary?—The author states that, although there is a generally changing picture of the frequency of tuberculosis in the majority of civilized countries today, it still represents a real threat to the life of children. He quotes the literature that from 3.5% to 13% of children who have the primary disease will die as a result of tuberculosis before they reach adulthood. It is also emphasized that between 86% and 97% of chronic tuberculosis occurring under 30 years of age results from the evolution of primary tuberculosis of the child. The controlled use of chemoprophylaxis of primary tuberculosis is still in a state of development, and, therefore, absolute figures cannot be given. However, in the work so far published, there seems to be a universal opinion that the number of deaths and complications attributed to tuberculosis are reduced in those patients who are treated adequately. The author does not state at what age he would not use chemotherapy, but it is the impression of the reviewer that at any time through adolescence when there is indication of the primary infection, chemoprophylaxis would be indicated. This would be true whether the evidence of infection is a positive tuberculin test or whether there is a radiologic evidence of the infection. Treatment should be given at once since it is in the early stages of the disease that tubercle bacilli multiply rapidly and disseminate. The author further states that discovery of infection in the young child by tuberculin testing in a community survey is of great value in alerting the search for the infecting adult who is often unrecognized until that time.

Neue Oesterreichische Zeitschrift für Kinderheilkunde, Vienna

Abstracted by Hermann Vollmer, M.D.

3, No. 4, 1958

° Symptomatology and Serology of Ornithosis in Childhood. F. Müller and E. Mannweiler.—p. 269.
Experience with 227 Exchange Transfusions. K. Kundratitz and H. Gross.—p. 285.
Localization of Segmental Pneumonia in Childhood. W. Kircher and H. Messner.—p. 295.
Ellis-van Creveld Syndrome. H. Rössler.—p. 301.
Partial Factor V Deficiency. E. Deutsch and E. Zweymüller.—p. 313.
° Effect of Carbonic Anhydrase Inhibitors on the Electroencephalogram of Epileptic Children. A Rosenkranz and G. Roth.—p. 321.
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Differential Diagnosis of Dystrophy in the First Year of Life. K. Kundratitz and O. Stur.—p. 349.
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Sympathoblastoma Glandulae Suprarenalis. H. Gross.—p. 361.

Symptomatology and Serology of Ornithosis in Childhood.—Two cases are reported and the literature is reviewed. Ornithosis occurs at any age including early infancy. Its course can be as severe in children as in adults; encephalitis may occur as complication. Every child with atypical pneumonia and a positive Wassermann reaction should be suspected of ornithosis. Complement-fixing antibody titers of at least 1:16 which are subsequently rising are diagnostic. Titers in the pediatric age group do not rise as high as in adults.

Effect of Carbonic Anhydrase Inhibitors of the Electroencephalogram of Epileptic Children.—Intravenous administration of 10 mg/kg. acetazolamide (Diamox) did not change the electroencephalogram of 10 children with idiopathic epilepsy. Alkali reserve was reduced by this carbonic anhydrase inhibitor in most instances.

New England Journal of Medicine, Boston

Abstracted by Demetrius G. Traggis, M.D.

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Acetazolamide and Chlorothiazide in the Treatment of Ascites Due to Cirrhosis of the Liver. R. M. Myerson, R. E. Stout, and A. L. Forte.—p. 28.

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The Gamma Globulins and Their Clinical Significance: IV. Therapeutic Uses of Gamma Globulins. P. A. M. Gross, D. Gitlin, and C. A. Janeway.—p. 170.

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° Syndrome of Acute Osteomyelitis of the Superior Maxilla in Early Infancy. H. Lieberman and J. Brem.—p. 318.

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Proctology. E. P. Hayden.—p. 420.

° An Anaphylactic-Type Reaction Attributed to Penicillinase: Report of a Case. S. Caputi Jr.—p. 432.

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Bone-Marrow Failure Due to Relative Nutritional Deficiency in Cooley's Hemolytic Anemia: Painful "Erythropoietic Crises" in Response to Folic Acid. J. H. Jandl and M. S. Greenberg.—p. 461.

Modern Psychiatry and the Health Plans. D. G. McKerracher.—p. 474.

Endoscopy (To be concluded). E. B. Benedict.—p. 478.

Brief Recording: Candida Albicans Peritonitis Successfully Treated with Amphotericin B. D. A. Ohlwiler and E. M. Bricker.—p. 488.

A Comparative Study of the Effect of Transfusion of Fresh and Preserved Whole Blood on Bleeding in Patients with Acute Leukemia.—The authors carried out a study designed to attempt to settle the problem as to whether or not fresh plastic bag blood was more effective than bank blood in controlling the bleeding associated with leukemia. This bleeding was associated with thrombocytopenia. To do this the patients who had only had external visible bleeding were utilized for the study. Neither the physician nor the patient knew whether he was receiving fresh blood or bank blood. This was sent over by the blood bank according to a set program without the physician knowing which the patient was getting. It was also arranged that the patient help serve as his own control. If he received fresh blood the first time, he was then given bank blood the second time. Patients weighing under 45 kg. received 450 cc. of blood and patients weighing over 45 kg. received 900 cc. of blood. Both bank blood and fresh blood were transfused in plastic platelet recipient sets. The authors found that practically all of the hemorrhages had ceased after blood transfusion with fresh whole blood. In discussing this the authors pointed out that the increase in circulating platelets following fresh blood was significantly greater than that following bank blood transfusion. However, the magnitude of these increases was small, the main increase being 5,000 and the maximum being 22,000 per cubic millimeter. The highest rise in any patient was still far below the 50,000 platelets per cubic millimeter which the authors consider as the level above which hemorrhage does not usually occur. The authors also pointed out that other studies of whole blood coagulation and studies of prothrombin consumption did not show any changes in these patients.

Thyroglobulin Antibodies in Multiple Thyroid Diseases.—The recent discovery of circulating thyroglobulin antibodies in patients with Hashimoto's thyroiditis and spontaneous myxedema has led to the theory that autoimmunization to autogenously released thyroglobulin may be a causative factor in those diseases. Animal work has also shown the production of thyroiditis by the injection of homologous thyroglobulin and the production of antibodies to it. With this in mind the authors investigated several other forms of thyroid disorder for the presence of thyroglobulin antibodies. A control series was also used in which the patients were thought to have no evidence of thyroid disease. Two techniques of demonstrating these antibodies were used; however the red-cell hemagglutination technique appeared to be very much superior to that of the agar-gel precipitation method. Of 219 controls only 8 were shown to have any antibodies. Of 161 patients with various thyroid diseases 54 were shown to have antibodies. Antibodies were found in 34 of 94 patients with thyrotoxicosis,

in 7 of 10 with spontaneous myxedema, in 8 of 19 with nontoxic nodular goiter, in 3 of 5 with chronic thyroiditis, in 1 of 2 with subacute thyroiditis, and in 1 of 18 with athyrotic cretinism. In a small number of patients with acute thyroiditis, thyroid carcinoma, diffuse goiter, and adolescent goiter, no antibodies were demonstrated. The postulated mechanism for the production of these antibodies is that an insult to the thyroid gland liberates thyroglobulin from the thyroid follicle. Thyroglobulin is not normally present in the circulation. The subsequent reaction of the antibody to the antigent then produces lymphocytic replacement or destruction of the thyroid cells or both. The authors noted a high incidence of penicillin hypersensitivity according to the past history in many of these patients. In screening the sera for penicillin antibodies, as well as for thyroglobulin antibodies, both types were found in some patients. However, appropriate absorption methods appeared to show that the antibodies were specific to each substance. There was no cross reaction. The authors believe that the reason for the increased incidence of hypersensitivity to penicillin in these patients was that this particular type of patient had the ability to respond easily to a variety of ordinarily weak antigens. The authors noted also, as others had found, that patients with antibodies tended to have slightly higher globulin levels. The authors feel that this production of antibodies may be responsible for some cases of cretinism. They also suggested that this production of antibodies in thyrotoxicosis might be a method of helping to control the disease by its autodestructive effect on the thyroid gland.

Comment: This paper and the one following it, in the same issue of the *New England Journal of Medicine*, lend further support to the importance of the finding of antibodies to thyroglobulin. The implication of the destructive effect of these antibodies appears to be very suggestive. In a recent paper, given before the Society for Pediatric Research, one of the authors (R. M. Blizzard) reported on studies in several cases of cretinism. His studies were on mothers and their athyrotic cretins. Both the sera of three mothers and their cretinous offspring (up to 2 weeks of age) showed antibodies; antibodies were present in the sera of two mothers, but not in their cretinous offspring who were 3 and 9 years of age at the time; antibodies were found in the sera of two cretins, ages 5 and 6, but not in their mothers; antibodies were found in the sera of six mothers with normal infants. These studies suggested that in certain cases of athyrotic cretinism the placental transfer of maternal antibodies to thyroglobulin might produce destruction of the fetal thyroid. The exact mechanism by which the human produces antibodies to its own thyroid tissue is not yet clear.

Cat-Scratch Fever Associated with an Osteolytic Lesion.—The authors report the second case of an osteolytic lesion apparently associated with cat-scratch fever. The patient was a 4-year-old boy, who first developed pain in the right knee associated with low-grade fever, three days before admission. Two days later a maculopapular rash was noted and a few days later a swollen cervical lymph node. He had played often with cats and had been scratched by them. Positive physical findings were a firm, swollen, left anterior cervical lymph node, a fading rash, a mild limp favoring the right leg, and slight pain on full abduction of the right hip. All tests essentially were negative except a strongly positive cat-scratch skin test. Seventeen days after admission the gland became fluctuant and was drained. The purulent material was negative on culture. Cat-scratch skin antigen produced from it gave a strongly positive reaction in a known case of cat-scratch fever. Twenty-eight days after admission, because of persistent pain in the right leg, an x-ray was taken and revealed an osteolytic lesion with slight periosteal reaction in the intertrochanteric area of the right femur. A needle biopsy revealed material that was negative on culture but on microscopical examination revealed granulomas with central necrosis surrounded by epithelioid cells and lymphocytes such as is seen in cat-scratch disease. Treatment was by cast. In about two weeks healing was beginning, and five months later progressive healing was still present on x-ray. Antibiotics had been tried with the usual lack of success on the cervical gland. The authors felt that because of the negative cultures and the positive microscopical picture the diagnosis of the osteolytic lesion as that of cat-scratch fever seemed probable.

Syndrome of Acute Osteomyelitis of the Superior Maxilla in Early Infancy.—The authors present two cases of acute osteomyelitis of the superior maxilla. One was in a 3-week-old and the other in a 2-week-old child. Both were associated with Staphylococcus aureus, resistant to penicillin, streptomycin, and the tetracyclines. The authors feel that these

cases present in such a way that they produce a syndrome which can be recognized if one is aware of it. Both cases presented with fever and swelling of one side of face, nose, and orbit. The eye was proptosed in each and was immobile; chemosis was present. A mucopurulent nasal discharge was present, chiefly on the affected side. Initial x-ray showed density of the ethmoid area of the affected side. In one case x-ray repeated in one month showed an ovoid bone defect in the orbit. In both cases surgery was necessary on several occasions. In the first case a fistula developed from the alveolar process of the maxilla through which two small spicules of bone were sequestrated. In discussing this condition the authors found 80 cases reported up to 1949. The onset is as described. Fistula may form at the alveolar process of the maxilla, at the canine fossa, or near the inner canthus of the eye on the involved side. Tooth buds may be extruded with the drainage. Vomiting and diarrhea were usually present. In almost all cases S. aureus was recovered from the purulent discharge. Infection is thought to be hematogenous or from the nose into the maxillary sinus and to the tooth buds (maxillary sinus bony case not completely closed in the infant). Occasionally, besides the loss of permanent teeth, involvement of the orbit may lead to visual defect. The authors emphasize the seriousness of the condition and the need for immediate, vigorous, and prolonged treatment (because of the tendency for the infection to smolder). Both of their cases had a recurrence.

An Anaphylactic-Type Reaction Attributed to Penicillinase: Report of a Case.—The author reports a case of a 5-year-old child who developed a penicillin reaction for which she was given 800,000 units of penicillinase. Within a few minutes she developed marked dyspnea and acted as if she had chest pain. She appeared to be in shock. The entire gluteal area where the injection was given became swollen and red. Epinephrine, steroids, and antihistamines successfully treated the reaction. She had not had penicillinase before. The author points out that penicillinase is a protein enzyme obtained from bacteria. He hypothesizes that the widespread use of penicillin has produced penicillin-resistant bacteria which produce penicillinase. The harboring of these strains by an individual may lead to the development of sensitivity to penicillinase.

News and Comment

GENERAL NEWS

National Foundation Grants.—The National Foundation on July 15 announced allocations of more than $1,000,000 in March of Dimes funds for education in the health professions, including an appropriation for a new fellowship program to give doctors more extensive clinical training in the fields of rheumatology and birth defects.

Awards for education in the health fields are in addition to grants made for the same period in research and clinical investigation. The combined sum awarded is more than $3,500,000, according to Basil O'Connor, president of The National Foundation, originally the National Foundation for Infantile Paralysis.

Today's awards bring the total sum channeled into education for the health professions by The National Foundation to almost $32,000,000. Included in the $32,000,000 are funds for a Health Scholarship program initiated earlier this year to provide four-year college training for young Americans in five of the health fields—medicine, nursing, physical therapy, medical social work, and occupational therapy. The first 515 winners of these scholarships will be announced this summer.

The fellowship program announced today is open to residents or practicing physicians for study in rheumatology or in the treatment of patients suffering from birth defects of the central nervous system, both part of The National Foundation's new program. Fellowships will be awarded for a minimum period of one year but are subject to renewal. Stipends will range from $3,600 to $7,000 a year.

Commenting on the new fellowship program, Mr. O'Connor said, "To implement the expanded program of the The National Foundation we need people who are both interested and trained to do the job. Twenty years ago the underlying factor impeding progress in polio was lack of interest. This same factor is now impeding progress in the fields of birth defects and arthritis. In our experience, one of the best ways to stimulate interest is to help train the experts needed in the fight."

More than $900,000 of the educational grants announced today will go to universities, institutions, and professional associations to support the teaching and recruitment programs by which these groups are able to raise the standards of education and medical care throughout the nation.

Under these grants four medical schools—Yale, Western Reserve, Marquette, and Creighton—were awarded a total of $418,758 to press pilot studies on how best to train medical students to meet the fast changing patterns of disease. The National Foundation is now supporting this basic study in 14 medical schools across the nation.

Other grants will support a pioneering project at Duke University School of Medicine to develop motion pictures as teaching devices for medical education; give support to two new programs in physical therapy, one at the University of Indiana, the other at the University of Buffalo; and, allow Tuskegee Institute of Nursing to increase its student enrollment and teaching staff.

The following is a list of the new appropriation and grants:

Appropriation

To provide postdoctoral fellowships in the fields of rheumatology and birth defects: $65,000.

Grants

Yale University School of Medicine, New Haven: $99,906 to teach the concept and basic techniques of rehabilitation to medical students. The grant is for a three-year period.

Western Reserve University, Cleveland: $157,464 to teach the concept and basic techniques of rehabilitation to medical students. The grant is for a three-year period.

Marquette University School of Medicine, Milwaukee: $85,688 to teach the concept and basic techniques of rehabilitation to medical students. The grant is for a two-year period.

Creighton University School of Medicine, Omaha: $75,700 to teach the concept and basic techniques of rehabilitation to medical students. The grant is for a three-year period.

National League for Nursing, New York: $63,538 for additional regional conferences on rehabilitation nursing.

American Physical Therapy Association, New York: $81,000 to recruit physical therapy students, to provide consultant services to physical therapy schools, and to coordinate physical therapy education and practice with the medical profession.

National Association of Social Workers, New York: $58,587 to provide consultant services to improve education and practice of medical social work throughout the nation.

American Occupational Therapy Association, New York: $42,348 to recruit occupational therapy students.

Tuskegee Institute School of Nursing, Tuskegee Institute, Tuskegee, Ala.: $125,000 to increase student enrollment and teaching staff.

Meharry Medical College, Nashville, Tenn.: three grants totaling $61,610, divided as follows: In pediatrics, $20,500, to provide instruction for medical students and nurses; in orthopedic surgery, $25,600, to provide a teaching program and maintain a service department; in physical therapy, $15,510, to continue a service program and provide teaching staff for medical students and nurses.

Duke University School of Medicine, Durham, N. C.: $34,762 to develop motion pictures as teaching devices in medical education.

University of Southern California, Los Angeles: two grants totaling $32,057, divided as follows: In physical therapy, $18,709 to continue its undergraduate and graduate teaching program; in occupational therapy, $13,348, to provide instructors and to devise special equipment.

Indiana University School of Medicine, Indianapolis: $16,150 to develop its physical therapy program.

University of Buffalo, Buffalo: $11,676 to develop its physical therapy program.

Dr. Lincoln Receives Trudeau Medal.—The Trudeau Medal of the National Tuberculosis Association was presented on May 26 to Edith M. Lincoln, M.D., the pediatrician who started the chest clinic of the Children's Medical Service, Bellevue Hospital, New York, in 1922 and served as its chief until her retirement in 1956.

The medal was presented at an evening session of the National Tuberculosis Association held in connection with the 55th Annual Meeting of the NTA and the 54th Annual Meeting of its medical section, the American Trudeau Society, at the Palmer House, Chicago.

In presenting the award to Dr. Lincoln, Dr. W. L. Cooke, of Charleston, W. Va., chairman of the Trudeau Medal Committee, pointed out that clinical studies under the pediatrician's direction had had a profound influence in establishing the fact that tuberculosis meningitis can be cured.

"In the late 1930's," said Dr. Cooke, "studies on the chemotherapy of tuberculosis were begun by Dr. Lincoln, using Promizole, a synthetic sulfone. Dr. Lincoln and her associates added streptomycin to her studies shortly after it was introduced and they were soon engaged in trials of Promizole and streptomycin independently and in combination in the treatment of acute forms of tuberculosis in children. These investigations were among the most influential of the well-known studies that established the value of these drugs in the therapy of miliary tuberculosis and tuberculous meningitis in children."

Dr. Lincoln was one of the first to note that children with primary tuberculosis treated with isoniazid seldom, if ever, developed tuberculous meningitis. This had not been true of streptomycin.

Dr. Lincoln is the first woman to receive the Trudeau Medal since it was awarded in 1945 to the late Dr. Florence R. Sabin, anatomist who was for many years with the Rockefeller Institute for Medical Research, New York. The only two other women to receive the medal since it was first awarded in 1926 are Florence B. Seibert, Ph.D., who received it in 1938 while with the Henry Phipps Institute in Philadelphia and who had developed purified protein derivative (PPD), the substance widely used in tuberculin testing, and the late Miss Emily Bissell, sponsor of the first Christmas Seal Sale in this country.

Dr. Lincoln, in accepting the award, made the following remarks:

"I imagine everyone who has received the Trudeau Medal has felt as I do that there are so many other people who are more deserving of this great honor.

"It is a wonderful thing to receive a medal for doing just exactly what you wanted most to do. During the 34 years that I was in charge of the Children's Chest Clinic at Bellevue our small group of clinicians and investigators really had a good time and we looked forward

to rounds and conferences with eager anticipation. I am deeply indebted to these faithful co-workers, including the long succession of fellows made possible through the generosity of the American Trudeau Society. Most of these men and women have retained their interest in chest diseases in children and many are in charge of chest clinics in pediatric centers.

"After almost 25 years of study and observation our dreams were fulfilled by the development of successful antimicrobial agents. Only those of us who have lived through the years when a diagnosis of meningitis meant a death sentence, when 20% of the children who entered the tuberculosis ward at Bellevue died within a year, can realize the impact of the discovery of streptomycin. The end of an era came when the death rate from tuberculosis on our ward dropped below 1%.

"When antimicrobial drugs first became available it was obvious that a proper study of their action in children would mean devoting full time to the Chest Service. My husband gave me the encouragement and backing which permitted me to take the job as a volunteer.

"The pediatrician has been in the forefront of the fight against tuberculosis. Von Pirquet devised the first practical tuberculin test. Edwards Park, Bela Schick, and Charles Hendee Smith by their teaching and writing helped to counteract the belief that tuberculous infection in children was benign. Arvid Wallgren, Professor of Pediatrics in Stockholm, has had a profound influence on everyone interested in the diagnosis and prevention of tuberculosis in children. Armand Delille, French pediatrician, was the first to stress the importance of gastric lavage in recovering tubercle bacilli.

"To me this award is a recognition of the contributions of pediatricians in the fight against tuberculosis."

Specialists Certified by the American Board of Pediatrics.—The following candidates were certified as specialists by the American Board of Pediatrics, Inc., in San Francisco, June 19-21, 1959:

Ablin, Arthur Robert, Rafael, Calif.
Adkins, A. Thomas, Los Angeles.
Ahrens, Walter Edwin, Tucson, Ariz.
Allport, Robert Bradlee, San Rafael, Calif.
Arata, Nobby N., Whittier, Calif.
Arnold, Milton I., Torrance, Calif.
Asay, Lyal Duane, Fontana, Calif.
Austin, Glenn, Los Altos, Calif.
Austin, Wallace O., San Jose, Calif.
Ayala, Alfredo A., Albuquerque, N. Mex.
Ballenger, Claude N., Jr., Albemarle, N. C.
Biakanja, Krist Anton, San Jose, Calif.
Bick, Guenther Udo Claus, Santa Monica, Calif.
Bowen, Channing M., Spokane, Wash.
Campbell, Ralph K., Pomona, Calif.
Char, Florence, Berkeley, Calif.
Clark, Patricia M., Mill Valley, Calif.
Cohen, Melvin L., Phoenix, Ariz.
Compton, Alfred D., Jr., Vallejo, Calif.
Daeschner, George Lee, Houston, Texas.
Dale, Earle Philip, Encino, Calif.
Daschbach, Robert J., San Mateo, Calif.
DeMeritt, Ray Thurston, Richland, Wash.
Dituri, Bessie, Los Angeles.
Dominguez, Alberto M., Bakersfield, Calif.
Done, Alan Kimball, San Francisco.
Drescher, Alexander N., Fort Carson, Colo.
Dundenhoeffer, Frank E., La Canada, Calif.
Easton, James G., Manhattan Beach, Calif.
Feiertag, Richard B., Sacramento, Calif.
Fink, Burton W., Encino, Calif.
Fink, Howard D., New York.
Fisher, Delbert Arthur, Portland, Ore.
Harm, John P., South San Francisco, Calif.
Hayden, Patricia Wills, Seattle, Wash.
Hayden, Ralph Noble, Jr., Seattle, Wash.
Heimlich, Ernest M., Los Angeles.
Higgins, Lloyd G., Modesto, Calif.
Hill, William E., San Bernardino, Calif.
Holroyd, H. James, La Canada, Calif.
Howard, Harry Emerson, San Rafael, Calif.
Huffman, Phyllis, Midland, Texas.
Huitt, J. Dempsey, Honolulu.
Kellogg, Leonard Frank, Jr., Garden Grove, Calif.
Koel, Bertram Stephen, San Rafael, Calif.
Lavin, Sheldon Earl, Los Angeles.
Leach, Edwin Morse, Norfolk, Va.
Littlejohn, Clarence G., Los Angeles.
Marks, James F., Fort Sam Houston, Texas.
Marubayashi, Stanley T., Santa Ana, Calif.
McKean, Charles Mann, San Francisco.
McNiel, James Riley, Shawnee, Okla.
Michel, William Orison, Modesto, Calif.
Miller, Alan, N., II, Irving, Texas.
Moncrieff, Robert Wynne, Los Gatos, Calif.
Morrell, Don Lawrence, Denver.
Murphy, Richard Stock, San Diego, Calif.
Murray, John Preston, La Jolla, Calif.
Neumaier, Hildegard, Houston, Texas.
Oda, Ruth E., Hilo, Hawaii.
Olsen, Lyman J., Provo, Utah.
Orr, Marjorie Kathleen, Midland, Texas.
Peck, Eugene H., Oakland, Calif.
Peters, Richard R., San Bruno, Calif.

Rappoport, Stanley, Alhambra, Calif.
Regello, Marjorie Carlson, Richmond, Calif.
Robertson, John A., Pasadena, Calif.
Robinson, Tom W., Costa Mesa, Calif.
Saphir, Walter, Sunnyvale, Calif.
Sceats, Donald J., Pueblo, Colo.
Schaan, Robert Charles, Portland, Ore.
Schour, Marianne, Oakland, Calif.
Selby, George W., Glendora, Calif.
Shatkin, Eugene Parker, San Rafael, Calif.
Sindell, Harlan W., Miami Beach, Fla.
Stanton, Robert Earl, Van Nuys, Calif.
Stevenson, John L., Jr., Portland, Ore.
Stewart, Donald Rogers, San Jose, Calif.
Strick, Lawrence, North Hollywood, Calif.
Sumi, Walter Takeshi, Los Angeles.
Tandysh, Matthew A., Albuquerque, N. Mex.
Tietz, Walter, Fontana, Calif.
Van Rooy, Clemens W., Portland, Ore.
Victor, Arnold Baker, Jamestown, N. Y.
Waring, William Weston, Ukiah, Calif.
Weinberg, Horst D., Fresno, Calif.
West, William, Stockton, Calif.
Whiteman, Shirley T., Los Angeles.
Whyte, David, Lakewood, Calif.
Williams, Chester P., Sunnyvale, Calif.
Zoger, Seymour, San Francisco.

The following candidates passed their examination in New Orleans, in March, 1959, but were not eligible to receive certificates until July 1, 1959:

Abildgaard, Charles F., Cristobal, Canal Zone.
Batmanis, Elizabeth, Houston, Texas.
Brewer, Earl Johnson, Jr., Wharton, Texas.
Farber, Stuart D., New Orleans.
Hill, Robert Douglass, Fort Worth, Texas.
Johnson, Charles H., Jr., New Orleans
Jones, Jake, Jr., Shawnee, Okla.
Manson, Joseph Raymond, Baton Rouge, La.
McElhenney, Thomas R., Houston, Texas.
Nichols, Warren Wesley, Lake Charles, La.
Whitington, Gene Luther, Memphis, Tenn.

Special Foreign Certificates:

Ansari, Manzoor Alam, Giridih, Bihar, India.
Conde, Nicholas Cardenas, Caracas, Venezuela.
Dacanay, Eleonora Posadas, Quezon City, Philippines.
Ferrier, Pierre, E., Geneva, Switzerland.
Fikrig, Senih M., Istanbul, Turkey.
Halac, Elias, Jr., Cordoba, Argentina.
Lee, Ting-Chien, Chicago.
Moon, Hyung Ro, Seoul, Korea.
Nanda, Satya Pal, Kaushalpuri Kanpur, U. P., India.
Ozkaragoz, Kemal, Houston, Texas.
Parmanand, Mira, Bombay, India.
Puig, Jose R., Washington, D. C.
Quitangon, Leonardo Angeles, Maragondon, Cavite, Philippines.
Reid, Robert, Trujillo City, Dominican Republic.
Roldan, Erlinda Cruz, San Juan, Rizal, Philippines.
Tina, Leticia U., Manila, Philippines.
Yuceoglu, Ayse Munire, New York.
Paz, Felicisima G., Marikina, Rizal, Philippines.
Larios, Georgia C., New York.

ANNOUNCEMENTS

Mead Johnson Grants for Pediatric Research.—The Awards Committee for the Mead Johnson Program for Pediatric Research of the American Academy of Pediatrics announces the availability for the coming year of funds to provide financial aid to young pediatric research workers. These funds have been provided each year since 1958 by Mead Johnson & Company under rules established by the Academy's Awards Committee. The maximum amount for any one grant in any year is $3,500. Grant applicants should be young pediatricians who are not more than 10 years beyond the completion of their residency. These grants are specifically intended to encourage the young, unestablished, research-minded, academic pediatrician. Deadline for receipt of grant applications for July, 1960, will be January 15, 1960.

Interested persons should write to American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill.

Nutrition in Pregnancy.—A monograph of the five papers presented at the Symposium on Nutrition in Pregnancy in Columbia, Mo., Oct. 11, 1957, is now available. These papers, which were published in *The Journal of the American Medical Association*, include the following: "Nutritional State of the Mother Prior to Conception" by Genevieve Stearns, Ph.D.; "Maternal Nutrition and the Fetus" by Ray Hepner, M.D.; "Production of Congenital Malformations by Dietary Measures (Experiments in Mammals)" by Josef Warkany, M.D.; "Vanderbilt Cooperative Study of Maternal and Infant Nutrition: XII. Effect of

Reproductive Cycle on Nutritional Status and Requirements" by William J. McGanity, M.D., F.R.C.S. (C), Edwin B. Bridgforth, A.B., and William J. Darby, M.D., Ph.D.; and "Metabolic and Biochemical Changes in Normal Pregnancy" by Icie G. Macy, Ph.D., Sc.D. The "Nutrition in Pregnancy" monograph may be obtained, free of charge, from the Office of the Council on Foods and Nutrition of the American Medical Association, Philip L. White, Sc.D., Secretary.

Kenny Foundation Scholarships.—The Sister Elizabeth Kenny Foundation announces continuation of its program of postdoctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of the neuromuscular diseases.

The Kenny Foundation Scholars will be appointed annually. Each grant will provide a stipend for a five-year period at the rate of $5,000 to $7,000 a year, depending upon the scholar's qualifications. Candidates from medical schools in the United States and Canada are eligible.

Inquiries regarding details of the program should be addressed to Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, Inc., 2400 Foshay Tower, Minneapolis 2.

Residency in Pediatric Oncology.—Applications for the Residency from July 1, 1960, to June 30, 1961, in Pediatric Oncology at Memorial Center for Cancer and Allied Diseases in New York will be received up to Nov. 1, 1959. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3,600 annually plus maintenance. For application forms and information write to Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21.

Positions in Infant Neurology.—Training in developmental pediatrics and infant neurology is available for Board-eligible physicians at the Clinic of Child Development of the Children's Hospital, Columbus, Ohio, on two levels. The first is a fellowship for physicians, preferably pediatricians, recently completing their residencies, with an opportunity to continue at faculty status in the teaching and research program. American citizenship is required. For those with additional qualifications, whether in pediatrics or in other fields, there is available a full-time staff appointment in the Department of Pediatrics of the Ohio State University College of Medicine, with major responsibility in teaching and research. For further information please write to the Clinic of Child Development, Children's Hospital, 561 S. 17th St., Columbus 5, Ohio.

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1. Edsall, G.; Altman, J. B., and Gaspar, A. J.: Am. J. Pub. Health, 44: 1537, 1954.

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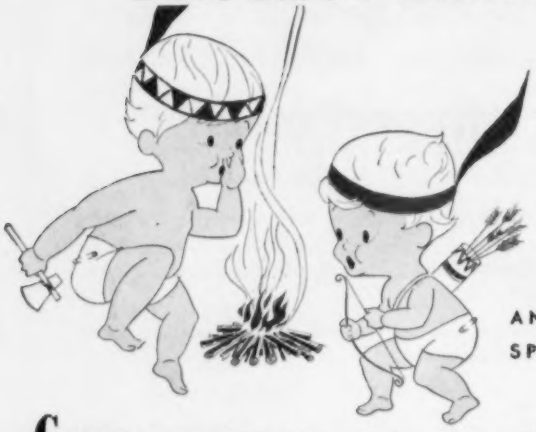

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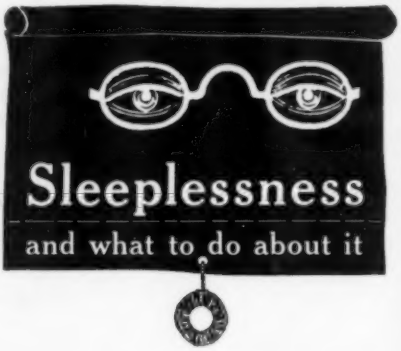

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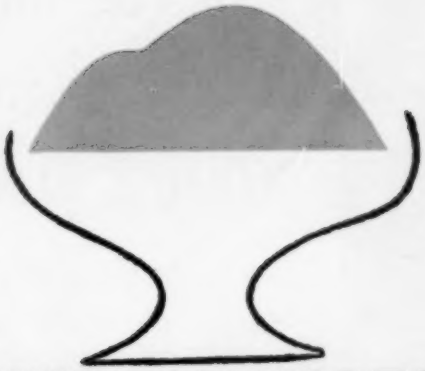

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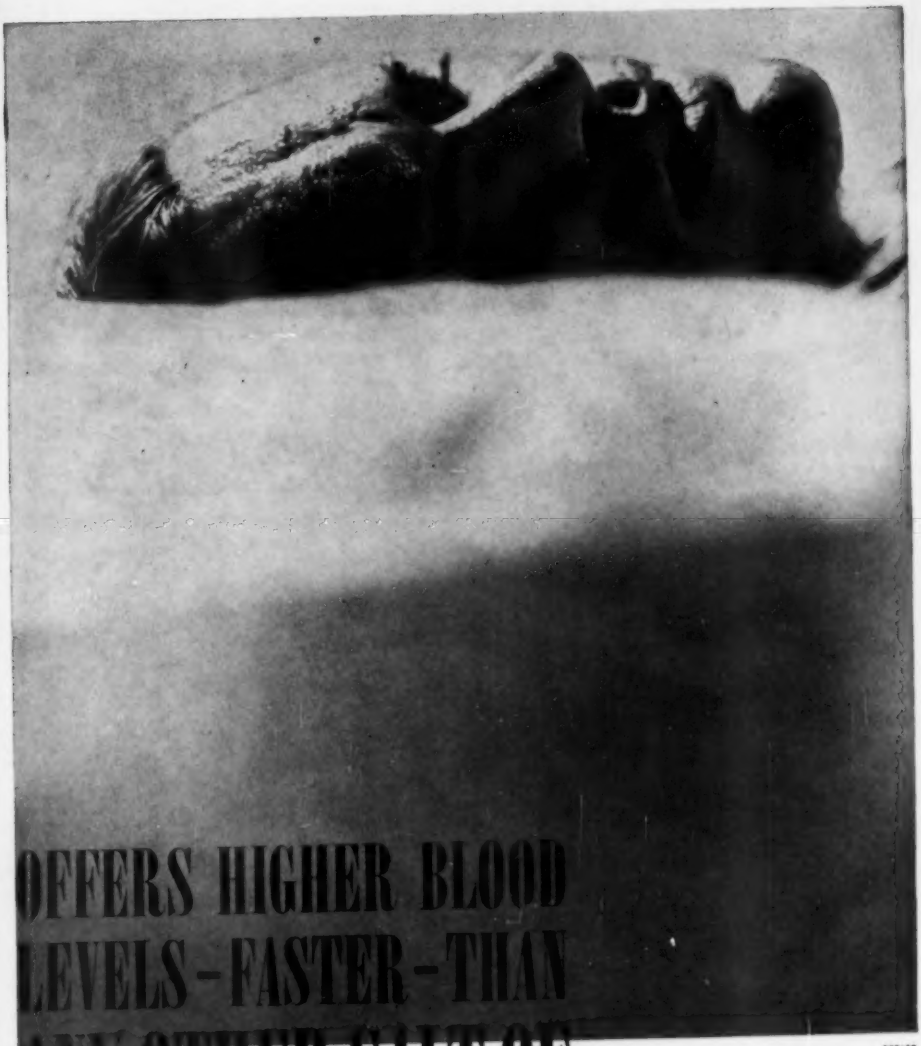

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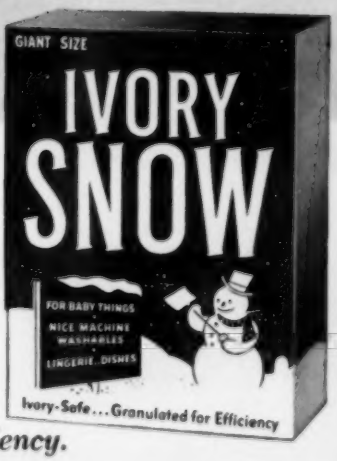

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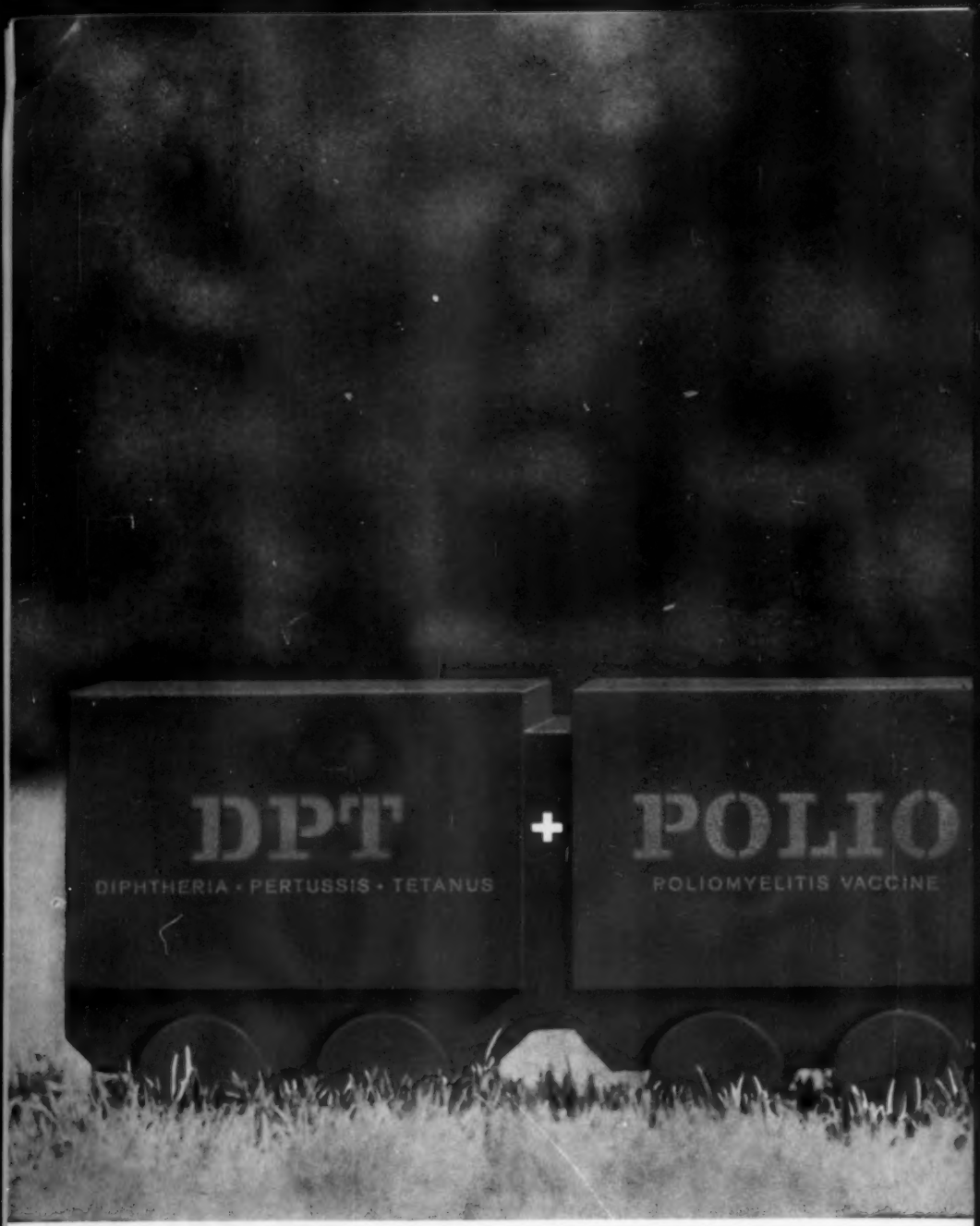

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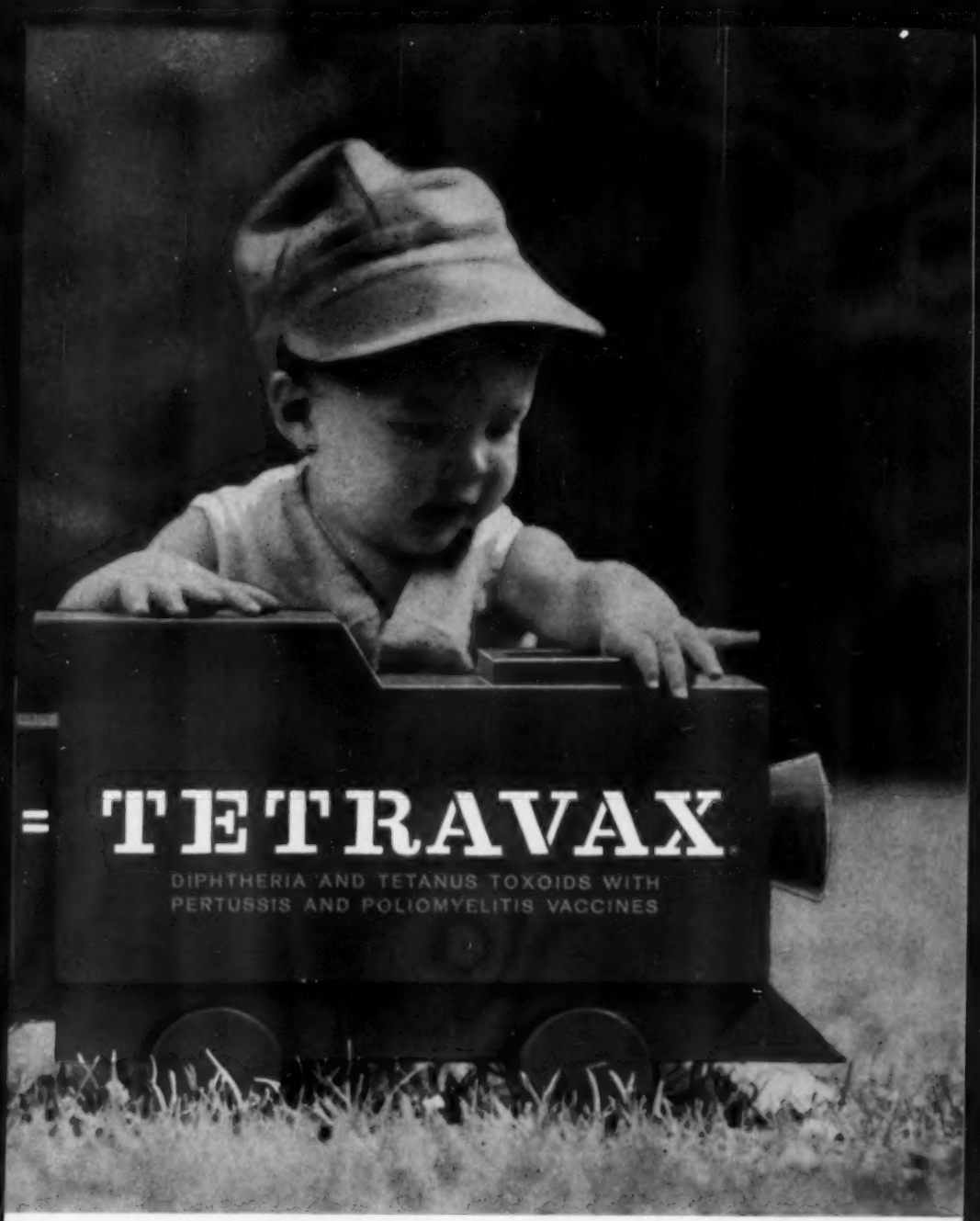

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Indications for Hysterectomy—Willis H. Jondahl, Harlingen, Texas—Lecture

Rheumatoid Arthritis—W. Paul Holbrook, Tuscon, Ariz. Panel Moderator

Colloidal Isotopes and Leukemia—Joseph M. Hill, Dallas—Lecture

Treatment of Diabetes—Randall G. Sprague, Rochester, Minn.—Panel Moderator

Infectious Diseases in Children—Harris D. Riley, Jr., Oklahoma City—Panel Moderator

Tranquilizers in Medical Practice—Stewart Wolf, Oklahoma City—Lecture

Surgical Approaches to Parkinson's Disease—William W. McKinney, Fort Worth—Lecture

Congestive Heart Failure—James V. Warren, Galveston—Panel Moderator

Peptic Ulcer in Rheumatoid Arthritis—Lloyd G. Bartholomew, Rochester, Minn.—Lecture

Immunization and Its Future—Blair E. Batson, Jackson, Miss.—Lecture

Children's Eyes—Tullos O. Coston, Oklahoma City—Lecture

Obstetrical Emergencies—Willis E. Brown, Little Rock, Ark.—Panel Moderator

Hernia Repair—Francis C. Usher, Houston—Lecture

Premarital and Marital Counseling—Oren R. Depp, New Orleans—Panel Moderator

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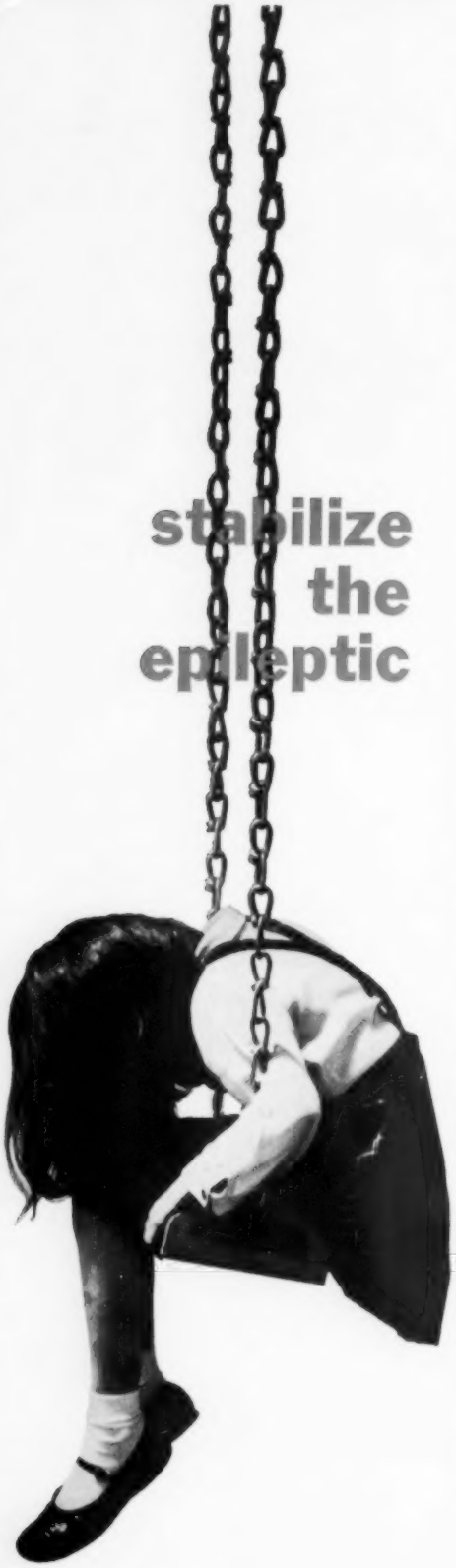

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